Pediatrics

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ORIGINAL ARTICLES

PRESIDENT'S ADDRESS

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THIS 19th annual meeting of the Academy marks the end of an eventful year. I reach the end of my stewardship with the hope that many important decisions of the past year will prove to be for the best interest of the Academy.

It is the privilege of this moment to philosophize and to express one's own opinions. Many of my predecessors have spoken of organizational aspects of the Academy. I should prefer first to speak a few words about the many individuals who comprise its membership. I like to think of the Academy as an association of those with kindred interests and with many bonds of keen personal friendship. I am happy that my lot has been cast with pediatricians and I am sure I share with all of you great enjoyment of the fellowship which has proceeded from our confraternity of interest.

The Academy exists only to express our mutual interest in childhood and to translate this interest into everything which can benefit the condition of childhood. We were early reminded by Dr. John Lovett Morse that we must strive to function not for ourselves alone and our history will well attest that the welfare of children and not the aggrandizement of our members has been the principle objective of this organization.

One who enters any profession does so with the expectation of contributing more to society than he will receive in return in terms of visible reward. The pediatrician may not wish to sentimentalize his concept of his profession but must recognize that the financial returns from his efforts cannot be compared with those provided by many occupations with an eight hour day and a five day week. Probably few would choose this branch of the profession on the basis of purely monetary reward.

Why then have you chosen this specialty in which the hope of financial emolument is far less than many other occupations and less than many other specialty fields within the profession of medicine? I suspect that this is because the practice of medicine with children gratifies so many of the feelings which lead one to a profession rather than to a business, to medicine rather than to another profession and thus finally to pediatrics among the many medical specialties.

Presidential Address given at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 18, 1950.

The love of children is, of course, not restricted to pediatrics or to pediatricians but there are many delightful things about the child as a patient. Pediatrics offers the opportunity to observe the growing organism and growth is a biologic function of unending fascination whether one observes it in a child or in a garden. The termination of pediatric care is the triumph of maturity which is in happy contrast to the medical care of aging adults in which the physician is eventually confronted with the final disasters of degeneration and death.

Much of the time of the pediatrician is devoted to the medical care of the well child with the supervision of nutrition, environment, immunization which affords the possibility of preventing many of the most serious diseases that formerly menaced the health of children. Our generation has witnessed a tremendous improvement in morbidity and mortality in infancy and in childhood. It is not altogether fair, of course, to attribute all or even much of this improvement to pediatrics alone for many agencies have contributed. We have been presented with new tools for diagnosis, for preventive care, and for treatment and at the same time have been aided by a great upsurge in public interest. Not only have we been presented with facilities to improve the medical care of children but we have also enjoyed public acceptance of these measures.

Childhood illnesses are not always simple but they are usually straight forward, susceptible to accurate diagnosis, and responsive to well designed treatment. There are, of course, plenty of psychologic disturbances and actual psychiatric diseases in childhood but, by and large, all childhood illnesses can be studied with more objectivity than in the adult for they are not apt to be a devious combination of physical illness complicated by the degenerative changes of aging, by fixed psychiatric overlay, by fear and worry, by oppressive circumstances. Furthermore the child, as a function of growth, has excellent reparative powers so that even serious illness frequently eventuates in complete restoration of function.

There are thus many reasons for entering the speciality of pediatrics, additional ones will occur to all of you, and by and large actual practice does not fall far short of pleasurable anticipation. The pediatrican has the opportunity for most gratifying relationships with his child patients and, because the child is the high spot of the family, he has the opportunity for a trusting and intimate relationship with the parents. He must perforce become the family advisor about many health matters. Probably he is more nearly the lineal descendant of the old time and frequently lamented family doctor than any other physician on today's scene. It is difficult today to recreate the horse-and-buggy doctor who knew all about everything simply because there was not nearly so much to know as there is with our present complexity of medical knowledge. Even so, the general practitioner of 50 years ago, however limited his technical knowledge, had the advantage of warm personal relationships which made him a valued advisor to the family. In many respects the pediatrician has succeeded to this position in the family.

There are those who insist that the pediatrician is simply a general practitioner in a special age group. This is hardly a fair statement. I have always thought that the only valid definition of a specialist is one who restricts himself to only those things which he does expertly. If the pediatrician is to be a specialist he must be adequately skilled in everything which he attempts to do and unless he restricts himself to those things for which he is fitted by training and experience he ceases to be a specialist.

What are the personal qualifications of a pediatrician? Fundamentally these are the same as in any branch of medicine. Honesty probably includes all the virtues and I hold

arrogance to be the greatest defect. A certain modicum of intelligence is helpful to one who must practice a learned profession, but to it must be added training and experience. As one's years of practice are prolonged, patience and endurance seem to be increasingly necessary but it is the parents and almost never the child who try these qualities.

How is the preliminary training of the pediatrician best constituted? This subject has been studied at length by the Board of Pediatrics and by many other responsible organizations. Three years of hospital training after medical school seems like a reasonable requirement but this time is best employed by breadth of training rather than by intensity of training. When the fundamental four years of medical education have been completed, the rudiments of pediatrics are readily imparted and special techniques are not too difficult to acquire. Three years had best not be devoted to learning the same things over and over. The sequence of a pediatric internship followed by two years of pediatric residency usually constitutes poor training for pediatric practice although, to be sure, many institutions have modified their residency program in recognition of the necessity for breadth of training.

The practice of pediatrics covers so wide a range and involves so many fields of knowledge that the pediatrician should profit from almost every bit of information which he can acquire. Pediatricians have their own compartment of knowledge but should embrace a multidiscipline approach in order to bring in contributions from other compartments of knowledge. The pediatrician will profit from some acquaintance with adult medicine, general surgery, nose and throat surgery, psychology, psychiatry, pathology, bacteriology and immunology, for the specialist in these fields has knowledge and techniques which can be applied to pediatrics. Nor need he limit his excursion outside pediatrics simply to other medical fields. Will he not profit from some knowledge of the humanities, of philosophy, economics, anthropology, or from such far removed biologic sciences as animal husbandry, plant pathology, veterinary medicine?

I mean to say that the pediatrician needs to enlarge and not to constrict his point of view. You will recall the statement of Martin Arrowsmith that he wasn't an educated man, he only went to medical school. Much of this breadth of education should be a function of the premedical years and very much of it may be acquired during the early years of practice, but it must be included in residency training.

Once in practice, the young pediatrician must first orient himself to his practice and to his patients. Sometimes this is a task for which his training has not well prepared him. A considerable time may elapse before he is properly equipped by experience with the innumerable details of every day practice; some of these things are trivial but others are of great importance. In his capacity as advisor and educator to the parents much of his early experience will be happy but, as we all know, some of it will be the reverse. At this point he must begin to assume his responsibilities to many things apart from his primary concern with his patients. One of the first of these is the Academy. Our members are the whole being of the Academy and the purpose of its existence is to advance the care of children in every way. To this end the Academy must contribute to the pediatrician opportunities for improvement of his knowledge through the medium of our scientific meetings and discussions, our publications and by the warmth of personal relationships within the organization. Through the years the Academy has increasingly met this responsibility by skillful planning and direction.

No less important is the contribution that each member must make to the activities of the Academy for these may comprise matters about which, alone, he can accomplish little.

There are silent areas in our membership which need to be explored for talent that may serve us well. Not only as an organization must we assume responsibility for those things which on a community or national scale affect the welfare of children but we must see to it that these responsibilities affect the consciousness of each fellow and involve his contributions to all functions within and without the Academy. Committee activities, liaison appointments and our relationship to other organizations concerned with child welfare must completely permeate our membership.

As the Academy has grown in stature and in importance it has become apparent that it cannot best serve the health of childhood by serving pediatricians alone. It was largely for this reason that the Study of Child Care was undertaken, an ambitious program which evoked great popular interest. You are all familiar with the Study and the contributions made to it by such men as John Hubbard, James Wilson, Warren Sisson, Glidden Brooks, to mention only a few among the very many responsible workers. This showed many excellent points in our system but it also revealed some deficiencies for which we must help to find an answer. Especially it was shown that improvement in the care rendered by pediatricians was not enough and that because a large percentage of children were cared for by general practitioners it was essential to expand and to improve the general medical school training in pediatrics. Interest in pediatric education has been an important outgrowth of the Study, so much so that I am hopeful that a section on education will hereafter be a part of our annual and regional meetings. Our interest in education as a means of improving the welfare of childhood must extend to all pediatricians, to the general practitioner and probably also to the public.

In such things as better training for the general practitioner, the pediatrician must devote himself wholeheartedly and unselfishly. Do we, by fostering better pediatric teaching for all physicians, simply build up our own competition? I think not, but what matter if we do! Our challenge is to encourage better and better medical care of childhood and to be ourselves best prepared to undertake it.

Our interest must extend to government and to governmental agencies. There are those amongst us who are suspicious and distrustful of such organizations as the Children's Bureau. This attitude will avail us little. Public health and private practice have each important functions which need not necessarily overlap. If we but each fulfill our own function and each define our sphere of activity our efforts should be not so much to exclude the Children's Bureau from those things which we believe to be our province as to aid and assist them in every way in the tasks which are their own. Surely there is no need for competitive overlapping.

This brings up another agency under governmental auspices, the Midcentury White House Conference on Children and Youth. It has been my privilege, with the support and approval of the Academy, to be a member of the National Committee and thus to realize the real implications and importance of this Conference. Its focus is to consider how we can develop in children the mental, emotional and spiritual qualities essential to individual happiness and to responsible citizenship and what physical, economic and social conditions are deemed necessary to this development. Many have asked, what has this to do with pediatrics? If we are willing to learn from other skills and to employ knowledge which originates outside our immediate specialty we must study these less tangible things which are apart from nutrition, growth and illness. We must examine ourselves to determine if we best contribute to these aspects of total health. How can we

really know the child and meet his problems unless we are willing to consider these factors which determine a healthy personality? To be sure, most of the work attempted by the Conference will be done by educators, the clergy, psychiatrists, lawyers, sociologists and by many others who are not concerned with pediatrics but if we are truly interested in the total welfare of the child we must contribute all we can to this effort. Best of all, we must examine our own practice to see if in our management of illness, injury, deformity, or simply of routine supervision we make a maximum contribution to the general welfare of children.

It is important for the pediatrician to recognize something of which he may be quite unaware: that his daily experience in the care of children provides him, if he will only avail himself of it, with an appreciation of these mental, emotional and spiritual values which he may think are beyond his concern as a physician. Leadership in these matters must originate from those who have experience with childhood and if the pediatrician shirks this responsibility he must expect many other things which he regards as directly his own concern to be controlled and directed by others.

We have still other responsibilities with respect to national matters. The social planners seem determined to inflict on this country some scheme of state medicine, call it whatever you may. As an organization we have disapproved this move and I believe that such action expresses the views of a very great majority of our members. In this we plead no selfish interest, although as citizens it would certainly be our privilege to do so, but we express only the conviction that any plan which has thus far been proposed would cause the care of children to suffer immeasurably. One need only to scrutinize a recent study of a committee of the American Medical Association reporting on the situation in England to feel assured that under any plan resembling the one in force in that country, private practice of pediatrics will practically cease. If we are correct in our belief that under our own system children are receiving good and constantly improving care, this would be nothing short of catastrophic.

I should like to conclude with the mention of a few things which concern the Academy as an organization. We have just completed reorganization of the Academy direction. This seems to involve no very profound changes. An Executive Secretary has been placed in the position of Secretary-Treasurer. The duties of this position have been redefined but delegated authority has not been notably increased. The Executive Secretary is appointed by the Executive Board and is responsible to it and thus in turn to the membership. Dr. Grulee, with hardly a change in facial expression, will automatically succeed to this position until his retirement.

The most important change is that all activities are to be centralized, no autonomous committees are to be set up and every committee and every individual who serves the Academy is to be responsible to the Executive Board and to the membership. It will be the chief responsibility of the Executive Secretary to supervise the central operation of the Academy, including business direction, to activate the work of committees and liaison officers, to attempt to provide funds from various sources necessary for the work of these committees and to integrate their responsibilities. It is my sincere conviction that a large and earnest membership can accomplish very much by this sort of directed endeavor.

This year we are faced with the retirement of Clifford Grulee which, in a way, seems surprising for his unfailing energy and ability have given no hint of his advancing years. Dr. Grulee has always seemed so much a part of the Academy and the Academy so much

a part of him that it seems incredible that there should be an Academy without him at the helm. No matter how we carry on, this change will not be easy to effect nor can it fail to cause some interruption of our smooth sailing. Never fear but we will continue to use his services for plans are already being made to this effect. Nor need we ever fear that he will fail to help us in every way possible in the future.

I wish that I could say the exact words which could express our feelings for Dr. Grulee. Probably this is not a matter for words. He need only look at this organization which stands today as evidence of his devotion, vision and industry. What greater tribute can there be than the sincere admiration and affection of our twenty six hundred members?

Nor would I fail to pay tribute to the great contributions which Edgar Martmer has made to this organization. Much of the success of organizational activities, the precision of regional and annual meetings, the variety and excellence of programs have been the product of devotion far beyond the call of duty. I am rejoiced to note that we are to continue to have the value of his experience and counsel on the Advisory Committee on Child Health, the Publications Committee and the Committee on Budget and Finance. We owe Dr. Martmer a debt for his services in the past which we will never adequately repay.

A successor for Dr. Grulee has been selected by the Board. This selection was made almost prayerfully and with a sense of deep personal responsibility. Advice was solicited, as you all know, from every possible source and was carefully heeded. The new Executive Secretary is to be Einor Christopherson. He is not well known to many of you and I hope that you have made this the occasion to meet him. I know that you will like him and the Executive Board is confident of his ability to serve this important post.

I should like to say a word in appreciation of the Executive Board. When I first served on this Board a number of years ago there was not a great deal to do. We elected new members, decided on relatively small expenditures, selected a meeting place and adjourned. In recent years, however, things have become much more complex. This organization has assumed great responsibilities and seems constantly to be taking on new tasks. Among other things the corporation is now a business of considerable magnitude which involves responsibility for great sums of money. I wish to express my personal appreciation for the sincere and unselfish labor which the members of the Board have devoted to their tasks and for the support which they have given to me.

You have honored me to make me your president. I have served in all humility with the idea that as an executive my personal opinions were unimportant. I have dedicated myself to making this an organization of all the members in which each should have a voice. I have solicited advice from all and have benefited from the advice which I have been freely given. I have been aware of some differences of opinion which are natural and healthy but I am unaware of any deep rifts in Academy solidarity.

My job in this past year has not been especially easy, but thanks to your unfailing response and support I have enjoyed every minute of it.

TREATMENT OF DISSEMINATED HISTOPLASMOSIS WITH ETHYL VANILLATE

By AMOS CHRISTIE, M.D., JAMES G. MIDDLETON, M.D., J. CYRIL PETERSON, M.D., AND DAVID L. MCVICKAR, M.D.
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THE demonstration in recent years that in the central portion of the United States and in certain other parts of the world histoplasmosis is a common benign infection[1, 2] has stimulated a greater interest in this disease. While it is true that the great majority of the infections with this fungus are benign to the point of being asymptomatic and clinically unrecognizable, it is also true that the increased interest in the infection is bringing to light many more cases of infection which are progressive, which either result in rapid destruction of the host as in the analogous process, miliary tuberculosis, or which are more slowly progressive to an ultimate fatal outcome. This is the course which has been followed by the great majority of the reported cases to date. However, there are also being recognized cases in which an intermediate degree of infection is found, cases where the dissemination of the infection has been arrested but where the patient may be moderately ill without showing the characteristics usually manifested by the progressive infections.

The present authors' experience with 35 cases of the progressive type, including those to be reported at this time, gives them considerable confidence in their clinical ability to separate the progressive cases from those with a milder degree of infection.

The hopelessness with which one must watch these progressive infections has led to widespread efforts at therapy. Almost every case report is, in fact, a report of the failure of one or many therapeutic agents.

Many drugs, including promine, actidione, penicillin, streptomycin, aureomycin, chloromycetin, sulfonamides, iodides, arsphenamine, mercurials, stilbamidine, and other antimony preparations have been tried in adequate doses by the authors and others without effect. Until the present study was undertaken no treatment had shown any capacity of influencing the downhill course of the infection with H. capsulatum in similar cases which were classed as disseminated and progressive.

In July 1948, Dr. Harry Lewis, of The Institute of Paper Chemistry, Appleton, Wis., called to the authors' attention a fungicidal compound—the ethyl ester of vanillic acid. This compound had been developed by I. A. Pearl[3, 4] as a by-product in the manufacture of sulphite pulp during the course of a research program pursued by the Institute on behalf of the Sulphite Pulp Manufacturers Research League. Experimental work done for the Armed Forces had shown it to have fungicidal properties for some of the fungi which produce spoilage of foodstuffs.[5]

Initial studies in the present authors' laboratory revealed the growth of H. capsulatum

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to be inhibited by ethyl vanillate in concentrations of 20 mg./100 cc. in plasma fortified media incubated at 37°C.

The purpose of this paper will be to review 18 months' experience with this chemotherapeutic agent in the treatment of generalized, progressive histoplasmosis.

Physical and Chemical Properties of Ethyl Vanillate

Ethyl vanillate (ethyl 4-hydroxy-3-methoxy benzoate) is a by-product of the sulphite pulp manufacturing process. It has a molecular formula of $C_{10}H_{12}O_4$, and the structural formula as shown in chart 1.

Ethyl vanillate is made by esterifying vanillic acid which can be obtained by oxidizing the lignin in the spent liquor from the sulphite pulp manufacturing process. It is a low melting, colorless, crystalline solid which may be distilled under reduced pressure to give a colorless viscous oil of 99% or greater purity. The oil may be supercooled below its

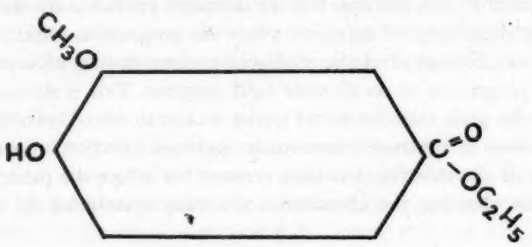

Chart 1

melting point of 43°C. and handled as a liquid at room temperature. The odor is slightly phenolic and it has a strong cinnamon-like taste. It is rather insoluble in aqueous preparations but quite soluble in organic solvents such as ethanol, propylene glycol, and carbowax, and is readily miscible with other oils. Its chemical nature lends it to all the reactions characteristic of a phenol and an aromatic nucleus.

A method of quantitative analysis of ethyl vanillate in blood, serum, and body tissues has been developed.* The exact chemical nature or the steps involved are not yet clear; however, it is believed the total molecule is measured including any conjugation that may take place *in vivo*. Since this test reproduces uniform results with known solutions of ethyl vanillate, it has served as a useful tool in following blood levels in patients and animals. The details of the test and reagents used are shown.

Reagents Required

5% copper sulphate solution
7% sodium tungstate solution
2/*N* sodium hydroxide
2/*N* hydrochloric acid
2/*N* acetic acid
p-nitroanaline reagent (30 mg. *p*-nitroaniline-3 cc. glacial acetic acid made to 100 cc. with distilled water)

* The fundamental principles of this method were suggested by members of the Institute of Paper Chemistry; however, the details of the method and its adaptation to micro studies for medical use were prefected by Dr. Ann. S. Minot, Department of Biochemistry, Vanderbilt University School of Medicine.

10% sodium nitrite solution

20% sodium carbonate solution

The detailed procedure for blood or serum is as follows:

1. 0.1 cc. of whole blood or serum is delivered quantitatively into a test tube containing exactly 4.9 cc. water. Mix.

2. Add 0.5 cc. 5% $CuSO_4$ and 0.5 cc. 7% sodium tungstate. Shake vigorously and let stand 5 min. or more and centrifuge.

This procedure precipitates the protein and removes any excess of $CuSO_4$ and results in a dilution of the 0.1 cc. of blood or serum to a total volume of 6.0 cc. After centrifugation the supernatant fluid is water clear and colorless and very slightly alkaline.

3. 3 cc. of the supernatant fluid is now placed in a dry, reasonably large test tube (NPN tubes were used) and 7.0 cc. of distilled water are added to bring the volume to 10 cc.

4. Now add 2 cc. of 2/*N* NaOH, mix, and heat in a boiling water bath for 5 min. (count time only after the bath resumes boiling after the transient cooling from the introduction of the tubes).

At the end of 5 min. remove tubes from bath and cool quickly by placing in a bath of ice water.

5. Without more delay than necessary for thorough cooling, add 2 cc. of 2/*N* HCl to neutralize the alkali and 1 cc. of water to bring the volume to 15 cc.

6. A blank tube is prepared containing 11 cc. of water, 2 cc. of 2/*N* NaOH, and 2 cc. 2/*N* HCl.

7. Now to the blank and the unknown add in the following order with mixing after each addition the following:

2 cc. of 2/*N* acetic acid

0.5 cc. of the *p*-nitroaniline reagent

2 drops of 10% nitrite and let stand exactly 2 min.

Then add 5 cc. 20% sodium carbonate and 2.5 cc. distilled water. (Bring total volume to 25 cc.)

Mix and let stand 30 min. before reading the color densities in a photoelectric colorimeter.*

A standard curve or standard constant factor is prepared by making a fresh solution of ethyl vanillate and running suitable aliquots of this through the entire procedure.

Depths of color suitable for reading in a final volume of 25 cc. are obtained over a range of 5-50 μg. of ethyl vanillate.

Colors from dilutions of ethyl vanillate carried through the above procedure follow Beer's law. (Distilled water alone used as a blank is not satisfactory.)

The aliquot used for color development in the protein-free solution derived from blood represents 0.050 cc. of blood and on this basis the ethyl vanillate in mg. per cent in blood can be readily calculated.

Preparation of Standard

Place 100 mg. of ethyl vanillate in a 100 ml. volumetric flask and add water to volume. (A few cc. of weak NaOH aids solution.) One ml. of this solution is equivalent to 1 mg.

One ml. of the above stock solution is diluted to 100 cc. with water to make a test solution containing 10 micrograms/ml.

The standard may then be inserted in the above procedure following Step 3.

Pharmacologic Properties of Ethyl Vanillate

Mammalian Reactions.—*In vivo* toxicity experiments reveal that the dosage and levels tolerated vary but little within a given species but vary considerably with different species. Depending on the amount of ethyl vanillate given, objective response in the animal varied from no visible effect with small doses to coma and death when larger quantities were given. Though some animals had convulsions, the effect was that of a general anesthetic and was similar in all instances whether administered orally, subcutaneously, intravenously or intraperitoneally. Moderate doses that initially revealed no significant changes, when repeated at intervals of 8 to 12 hours, produced increasingly more severe signs indicating an accumulative phenomenon. When administered orally as a 20 to

* Klett-Summersen photoelectric colorimeter with filter No. 54.

40% solution in olive oil, rats will tolerate 6.3 gm./kg. in single doses without ill effect. The approximate LD_{50} for the rabbit is 1.6 gm./kg. and for the guinea pig 2.2 gm./kg.*,[5]

It was found that the white rats could tolerate a maximum of 3 gm./kg./day orally for 18 days when administered in three divided doses. The maximum tolerated by the guinea pig was 1 gm./kg./day with similar administration. However, it must be pointed out that the act of administration is not without ill effects, for control animals receiving pure olive oil by gavage every eight hours had a poorer weight gain than did controls and microscopic study of their esophagi revealed local inflammatory response and areas denuded of epithelium.

Animals receiving larger, fatal doses had grossly evident hemorrhages from the mucosa of the upper gastrointestinal tract. Microscopic study uniformly showed hemorrhage into the necrosis of the mucosa of the upper gastrointestinal tract; thickening of the pulmonary alveolar walls with congestion, edema and round cell infiltration; evidence of glomerular irritation and tubular degeneration in the kidneys; myocarditis; and generalized engorgement of the capillary bed. Less consistent findings were fatty metamorphosis and focal necrosis of the liver. Some animals receiving the maximum tolerated dose had some thickening of the alveolar walls, myocarditis and minimal changes in the intestinal epithelium. Those receiving less than this amount, i.e., 1 to 2 gm./kg./day in the rat, had no demonstrable lesions by gross or microscopic examination.

From quantitative analysis it was concluded that approximately 10% of the ethyl vanillate orally administered in olive oil solution is unabsorbed or re-excreted in the feces (rat). Approximately 40 to 50% is recovered from the urine as ethyl vanillate or a conjugate.

When blood levels exceed 50 mg./100 cc. there is an abrupt increase in toxic manifestations, suggesting that changes which ordinarily take place are modified, i.e., that the liver is less able to conjugate the drug. Preliminary tests show that the ethyl vanillate, having once passed the portal circulation, is so modified as to be less fungistatic than an equivalent amount of unaltered drug.

Antibiotic Functions.—Ethyl vanillate has been found to inhibit the growth of several strains of micro-organisms *in vitro,* both bacterial and mycotic. This is reported elsewhere.[5] Among these organisms the fungi seem more affected and H. capsulatum is one of the most susceptible.[6] *In vitro* experiments carried out in serum or plasma fortified pour plates at 37°C. reveal H. capsulatum to be inhibited by ethyl vanillate concentrations of 20 to 30 mg./100 cc. While this is high in terms of other chemotherapeutic agents and their relation to the susceptible organisms, it falls within the range of levels attainable in the tissues and body fluids of experimental animals and man.

Considerable difficulty has been encountered in establishing histoplasmosis as a controlled infection in experimental animals. Different genera of the same order vary in their native resistance to the infection.

Because the virulence of the multiplying organisms vary from strain to strain and within a given strain, over a long period of time, a completely satisfactory mortality curve has not been produced. For this reason the present investigators have not sufficiently established the therapeutic value of ethyl vanillate in the experimentally infected animal.

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* On the basis of these and other tests performed by Kettering Laboratory of Applied Physiology at the University of Cincinnati Medical School, ethyl vanillate was accepted by the Food and Drug Administration for use up to 0.1% in Army foodstuffs.

Results of Ethyl Vanillate in Treating Human Cases

Though the preceding data is inadequate in determining the safety or value of ethyl vanillate in the treatment of fungal infections, the well recognized course of progressive disseminated infections with H. capsulatum has given the authors the temerity to use the drug in treating certain human cases of this infection.

At this time 12 consecutive cases of culturally proved histoplasmosis have been treated; these have been interpreted as being representative of the progressive disseminated form of the infection.

Of these 12 cases, 5 survived and have continued well to the present date. While it is conceivable that one or even two of these patients might have survived their infection without specific therapy, it is inconceivable that all this group could have survived. In all probability all would have died in a matter of a few weeks or months if left untreated. Table 1 lists these cases together with a summary of some of their salient features. The case reports of all the surviving patients and two of the nonsurvivors are given in some detail. Case 7 is given because he seemed to be a favorable candidate for treatment and yet his course was unfavorable. He also represents the only patient in whom was encountered a markedly adverse reaction to the drug, great enough to indicate the withdrawal of the drug, and in whom the drug could have been interpreted as having hastened the fatal outcome. The other patients who failed to respond were either so far advanced as to be nearly hopeless or were like Case 3, the other nonsurvivor whose case report is detailed. This child tolerated therapy well and received treatment over a long period of time but because of her ulcerative enterocolitis it was not possible to obtain blood levels at any time which could be expected to yield an inhibitory effect.

Case Reports

Case 1. D. G., an 8 mo. old white male infant, was admitted to Vanderbilt University Hospital with a chief complaint of fever and "large liver."

Six weeks prior to admission he began to run fever. Three weeks prior to admission he developed a hacking cough and diarrhea for a 3 day period. He was found to have hepatosplenomegaly by his family physician at this time.

Two weeks prior to admission he started to have dyspnea and tachypnea with increased cough.

One week before admission his physician noted that the liver and spleen were larger and a blood count revealed a neutropenia. He failed to respond to penicillin, became pale and weak, and lost weight. A presumptive diagnosis of leukemia was made.*

Examination on admission revealed an edematous, emaciated infant, weighing 7.1 kg. He was pale, in marked respiratory distress, and had severe generalized eczema. The abdomen was greatly distended and there was marked hepatosplenomegaly.

Laboratory studies showed Hgb. 6.5 gm./100 cc., RBC 1.84 million/cmm., WBC 12.3 thousand/cmm. with a normal differential. Cultures of the blood and bone marrow were positive for H. capsulatum.

He was given supportive treatment including penicillin and blood transfusions. He ran an irregular febrile course with temperature of 37.8 to 40.0°C.

After the diagnosis was established, treatment with .62 gm. ethyl vanillate/kg./day in divided doses was started. Subsequently, this dosage was stepped up to 1.25 gm./kg./day and finally to 1.55 gm./kg./day for the last 17 days of his 47 day course.

Blood and bone marrow cultures made 12 days after treatment was initiated were negative as were all subsequent cultures. Treatment was stopped 2 mo. after admission when he had become afebrile and had started to gain weight. Chart 2 summarizes his course.

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* D. G. was referred to this hospital by Dr. A. W. Rucker, Columbia, Tenn.

TABLE 1

Case No.	Race	Age	Sex	Condition on Admission	Diagnosis Established by			Treatment Started	No. of Days Positive after Treatment Begun			Duration of Treatment (days)			Date Seen
					Blood Culture	Marrow			Blood Culture	Marrow		Total	Adequate*	Outcome of Case	
						Smear	Culture			Smear	Culture				
1	W	8/12	M	Very poor	+	−	+	12/ 8/48	<14		<16	46	46	Well	3/10/50
2	W	4/12	F	Poor	+	+		3/ 2/49	2			2	0	Died	3/ 3/49
3	W	12/12	F	Fair	+	−	+	4/18/49	44		44	44	0	Died	6/ 1/49
4	W	41 yr.	M	Very poor	+	−	+	4/21/49	5		5	5	?4	Died	4/27/49
5	W	5/12	M	Fair	+	−	−	6/ 5/49	†			58	47	Well	12/23/49
6	W	9/12	M	Very poor		+	+	6/25/49	4	4	4	4	No Level	Died	6/30/49
7	W	5/12	M	Fair to Poor	+	+	+	9/30/49	25	25	25	21	15	Died	10/25/49
8	W	3 yr.	F	Poor	+	+	+	10/ 2/49	5	5	5	5	4	Died	10/ 7/49
9	W	5 yr.	M	Fair to Poor	−	+	+	10/12/49		<10	<10	41	32	Well	2/ 2/50
10	W	12/12	M	Fair to Poor	−	−	+	1/ 5/50	‡			49	34	Well	2/27/50
11	W	9/12	F	Good	−	−	+	1/25/50			<8	47	34	Well	3/13/50
12	W	1-5/12	M	Moribund	+	+	+	2/21/50	3	3	3	3	0	Died	2/25/50

* 20 mg./100 cc. or above ethyl vanillate in blood.
† Culture positive in Louisville Children's Hospital.
‡ Culture positive in Cincinnati Children's Hospital.

He has been seen at intervals over the past 18 months and has shown normal growth and development.

Case 3. J. F., a 1 yr. old white female infant, was admitted to Vanderbilt University Hospital with a chief complaint of "retarded growth."

Four months prior to admission she developed fever, cough and progressive weight loss. A month later H. capsulatum was isolated from the bone marrow and blood at Louisville Children's Hospital. She was given a month's course of aureomycin, penicillin and supportive therapy, including transfusions, without benefit and was referred here.*

On admission she weighed 5.0 kg., was emaciated, and had a protuberant abdomen due to marked hepatosplenomegaly.

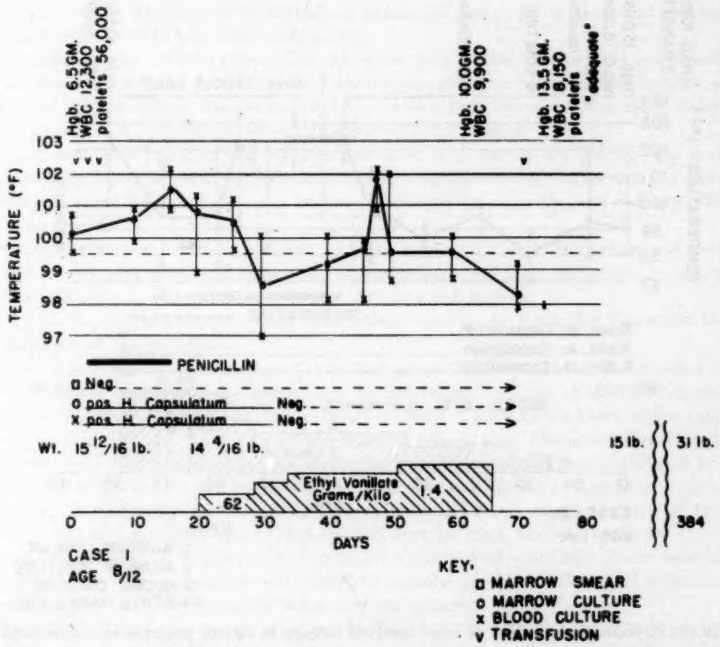

CHART 2. Favorable response to ethyl vanillate therapy in case of progressive disseminated histoplasmosis.

H. capsulatum was cultivated repeatedly from the blood and bone marrow. Treatment with ethyl vanillate, 1.2 to 1.9 gm./kg./day, did not yield blood levels above 8 mg. and when the dosage was increased vomiting ensued. The dose was, however, increased to high levels, 3.8 gm./kg./day in a vain attempt to obtain therapeutic levels. She had fairly severe persistent diarrhea with a low grade fever which increased after the 3rd wk. to become a septic fever with elevations to 39.4 to 40.5°C. She died on the 49th day after 42 days of treatment.

Autopsy revealed general histoplasmosis with extensive and marked gastrointestinal ulceration and extensive liver damage.

The clinical course of this case is illustrated in chart 3.

Case 5. W. H., a white male 5 mo. of age, was admitted to Vanderbilt University Hospital with a diagnosis of histoplasmosis made at Louisville Children's Hospital.

He had pneumonia at 6 wk. of age. Six weeks prior to admission he became irritable and the

* J. F. was referred here by Dr. L. T. Davidson.

following week the mother noted abdominal distention and afternoon fever. After 3 wk. he was taken to the Louisville Children's Hospital where hepatosplenomegaly, anemia, fever 40.0° C., and a positive histoplasmin skin test were found. A blood culture was positive for H. capsulatum and he was referred here for treatment.*

At admission he weighed 6.2 kg., was emaciated and pale, and had abdominal enlargement due to hepatosplenomegaly. Laboratory studies showed: Hgb. 8.5 gm./100 cc., RBC 2.91 million/cmm., WBC 8.1 to 4.2 thousand/cmm. during the 1st wk.

Ethyl vanillate therapy, .96 gm./kg./day to 1.92 gm./kg./day, yielded blood levels of 14 to 49

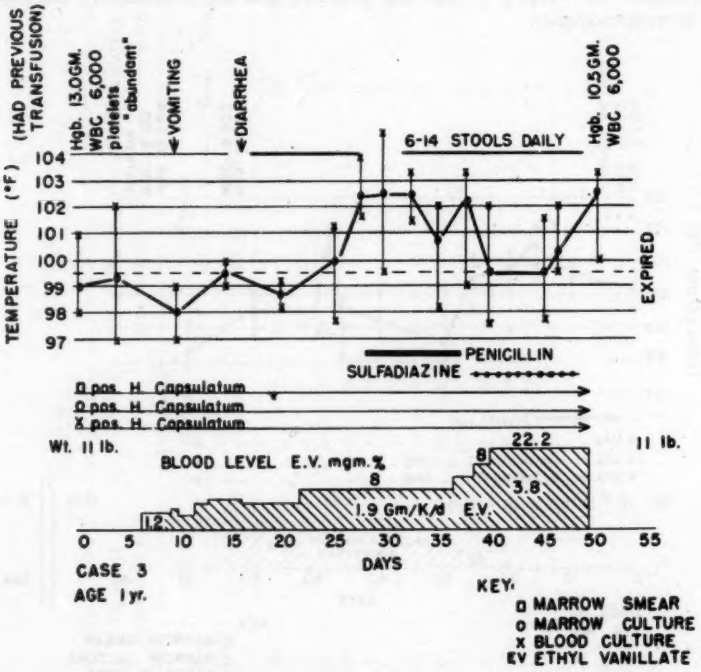

CHART 3. Example of failure of ethyl vanillate therapy in case of progressive disseminated histoplasmosis with extensive ulcerative enterocolitis.

mg./100 cc. The ethyl vanillate was well tolerated. He ran a low-grade fever for the 1st 4 wk. but he seemed to be improving slowly. He was treated for 58 days after which time he was fever free. The liver and spleen decreased in size during the treatment.

Two months after discharge his weight was 7.3 kg. He was beginning to talk. In the succeeding 11 mo. he continued to grow and develop normally. He is apparently well.

Case 7. A white male infant 5 mo. of age was admitted to Vanderbilt Hospital with a chief complaint of "splenomegaly, fever and irritability."

His physician had noted enlargement of the spleen at 2 mo. of age. At this time he had a hemoglobin of 9.1 gm./100 cc. In ensuing weeks there was gradual increase in size of the liver and spleen until 2 to 3 wk. before admission when there was rapid enlargement of spleen, increasing pallor, anorexia, fever to 40.5° C., anemia, leucopenia and thrombopenia. When a bone marrow culture yielded a growth of H. capsulatum he referred here for treatment.†

* W. H. was referred here by Dr. L. T. Davidson and Dr. Joe Little.

† This patient was referred here by Dr. L. T. Meiks of Indianapolis.

Treatment was begun immediately and an ethyl vanillate blood level of 56 mg. was obtained on the 3rd day with 2 gm./kg./day. The dosage was reduced to 1.3 gm./kg./day and the levels fell to 47 and after 3 days to 34. However, he developed clinical and chemical evidence of respiratory alkalosis, though the vanillate dosage had been decreased, and this persisted even when the blood level was 10 mg./100 cc. The drug was stopped. His course continued downhill and he died.

Autopsy findings were remarkable in that there was hemorrhage and necrosis located chiefly around the central vein of the liver and there was toxic degenerative changes in the proximal convoluted renal tubules in addition to the findings associated with the disseminated histoplasmosis.

Case 9. J. P., a 5 yr. old white male child, was admitted to Vanderbilt University Hospital with a chief complaint of headache and stomach ache.

He had been pale for 5 mo. and for 2 wk. had had fever, anorexia, weight loss, progressive paleness and weakness. On examination he showed, in addition to pallor, shotty nodes and hepatosplenomegaly 3 to 4 finger breadths below the costal margin.

His hemoglobin was 7.5 gm./100 cc. and the white cells numbered 800. This neutropenia persisted throughout his hospital course. H. capsulatum yeast cells were found in bone marrow smears. The first bone marrow culture was contaminated but another bone marrow culture made 4 days later did yield a growth of H. capsulatum. Blood cultures were never positive.

Treatment with ethyl vanillate was initiated and doses of .5 gm. to 1.4 gm./kg./day were well tolerated, yielding blood levels of 8 to 20 mg./100 cc. Two transfusions for anemia and leucopenia were given, on the 22nd and 42nd days. He was discharged as markedly improved after 49 days, 42 days of treatment.

Four months after admission, he weighed 19.5 kg., a gain of 2.3 kg. His spleen and liver were smaller and he was well. WBC had risen to 6.5 thousand/cmm. and Hgb. was stable, 11 gm./100 cc. He had been afebrile and without malaise. He has continued well to date.

Case 10. G. G., was a 6 mo. old white male infant, admitted to Vanderbilt University Hospital with a diagnosis of histoplasmosis.

When he was 2 mo. of age the mother, who had placed him in a nursing home, noted that he had lost weight and was pale. Home therapy was not helpful and at 3 mo. of age he developed mild diarrhea and vomiting. He was admitted to the Cincinnati Children's Hospital where supportive treatment was successful and he was discharged home to return to the Outpatient Department. During a succession of return clinic visits an increasing hepatosplenomegaly was noted and he began to spike a fever each day. He was readmitted to the Cincinnati Children's Hospital at 5 mo. of age and found to be moderately anemic with hepatosplenomegaly. Bone marrow cultures at that time were positive for H. capsulatum and he was referred here for ethyl vanillate therapy.*

Physical examination on admission here revealed a fairly well nourished infant who did not appear seriously ill. The examination was essentially negative except for abdominal distention with hepatosplenomegaly 4 to 5 fingerbreadths below the costal margin.

Ethyl vanillate therapy was started at 1 gm./kg. in 24 hr. in divided doses. Levels of 20 to 30 mg./100 cc. were obtained and he was maintained on this therapy for 42 days. He tolerated his treatment well. While under treatment the liver and spleen decreased in size. He was apparently entirely well when treatment was stopped. He was beginning to gain weight when he was discharged after 8 hospital weeks.

Case 11. G. M., a white female infant 10 mo. of age, was admitted to Vanderbilt University Hospital for an acute pharyngitis and otitis media. While she was in the hospital it was noted that she had a rather large liver, a palpable spleen and a positive histoplasmin test. Because of this a bone marrow culture was made. No organisms were seen on the bone marrow smear at that time and she was discharged. One week after discharge, the culture taken on admission day grew out H. capsulatum and the patient was readmitted. After discharge she had continued to run a fever from 38.3° to 38.8° C. and seemed listless.

Physical examination revealed a well developed and well nourished white infant of stated age who appeared acutely ill and in considerable distress. She was irritable. Physical examination was negative except for the residual pharyngitis and otitis media and slight abdominal distention. The spleen and liver were 2 to 3 cm. below the costal margin.

Two days after readmission, the patient was started on ethyl vanillate in doses of first 1.0 and

* G. G. was referred here by Dr. Sara Woods and Dr. Katharine Dodd.

then 1.5 gm./kg./day in divided doses. Blood levels of 20 to 30 mg./100 cc. were obtained 10 days after treatment was begun and were maintained to the end of treatment at 47 days. Bone marrow cultures were positive for H. capsulatum 2 days before admission and 8 days after, but 18 and 28 days later the cultures were negative. After the 1st 2 wk. of treatment she was afebrile and her liver and spleen decreased in size but she did not gain weight until after treatment was stopped.

Method of Administration of Ethyl Vanillate

The administration of ethyl vanillate presents several serious problems. The drug is a solid with a pungent phenolic odor and causes a burning sensation to the mucous membranes of the mouth. To give the drug in multiple gram doses necessary every 4 to 6 hr. is a real problem. With adults it is conceivable that it could be given in capsules or as a covered pellet, but with infants the only

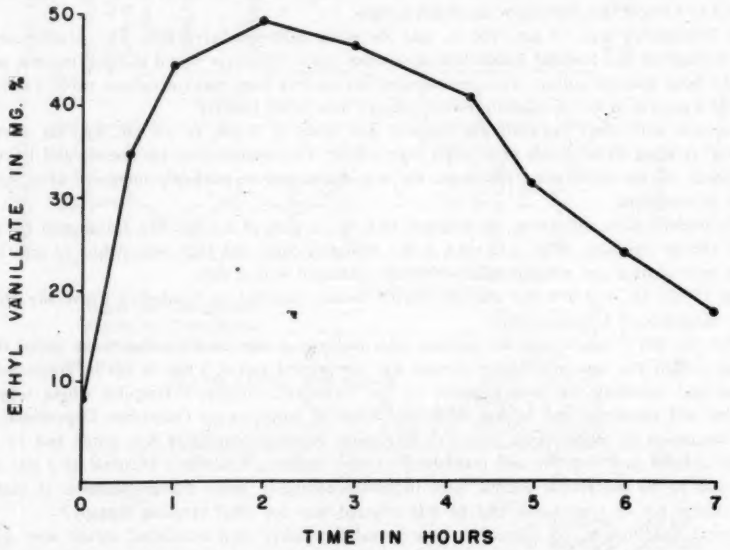

Chart 4. Persistence of ethyl vanillate blood levels following single test dose of .36 gm./kg. body weight, 6 hr. after preceding therapeutic dose.

feasible method of administration is to give it in solution. The drug is soluble in olive oil and after some trial and error it was found that a 40% solution is the most practical preparation. This remains liquid when kept at 37° but solidifies when put at room temperature. While the drug separates from the oil at the pH of gastric fluids, the oil apparently prevents any appreciable discomfort or disturbance from the effects of the drug upon the gastric or intestinal mucosa. It was found necessary to give the oil solution by gavage and to try to make the interval coincide with the feedings which can be given simultaneously. Though the drug can also be given dissolved in aqueous methyl cellulose solutions, the large doses needed are better tolerated in the oily solution. The local irritation from the drug precludes its intravenous or subcutaneous administration.

The gavage of the medication is not as much of a problem as it would seem at first thought because many of the children have anorexia to the degree where forced feedings are needed. In small infants the use of a small indwelling polyethylene tube may have an advantage over the repetition of the intubations.

In preparing the feedings for the children, it should be noted that the oil vehicle will supply a large proportion of the needed fat intake.

From the authors' limited experience it would seem best to start with small doses and increase to higher levels gradually so as to avoid high blood levels. In infants without diarrhea, 1.5 gm./kg./

day divided into 4 to 6 doses appears to be the upper limits of the dose and will usually provide blood levels of 20 to 30 mg./100 cc. Levels of this degree have apparently been effective therapeutically while levels of more than 40 mg./100 cc. have been associated with stimulation of the respiratory center and other undesirable toxic reactions. These are discussed in detail below.

It is suggested that the initial dosage should be 0.5 gm./kg./day in divided doses and that this be increased in steps of .5 gm. every 5 to 6 days until a dosage of 1.5 gm./kg./day or the desired blood level is attained.

In adults smaller doses of the drug should be used, probably less than 50% of the dose used in infants, as calculated on a weight basis. Another and better basis for calculating the adult dose would be to relate it to the surface area. The doses the present investigators have given are equivalent to about 5 gm./m^2 body surface/24 hr. for the maximum dosage.

Where severe diarrhea is present, it may be necessary to give doses which are much greater than could be tolerated by individuals with normal gastrointestinal tracts and absorption.

The peak blood level is reached in 3 to 4 hr. after oral administration and falls off fairly rapidly, so that therapeutic levels are not maintained more than 5 to 6 hr. with doses which do not exceed toxic levels. A characteristic absorption curve is shown in chart 4.

The narrow margin between doses required to give therapeutic levels and those which produce toxic manifestations makes it imperative to have adequate laboratory controls whenever this drug is to be used therapeutically. The authors' experience has indicated that one should proceed with caution and that it is better to take 1 to 2 wk. to work up to therapeutic levels than to attempt to achieve them early.

The time needed for treatment is not clear. The tissues have been rid of culturally demonstrable organisms in periods as brief as 8 days but where one is dealing with a chronic granulomatous process it may require long periods for the drug to reach relatively avascular areas. The authors have attempted in these cases to maintain therapeutic levels for a minimum of 42 days, though it is realized that this may represent over-treatment.

Toxic Manifestations and Side Effects

All the infants have shown slight drowsiness, apathy and inactivity persisting in some degree throughout the treatment period but from which they have completely recovered when the drug was stopped. Three patients developed sudamenous rashes which may have been due to excessive perspiration. One patient, at the end of the course, developed a fever presumably attributable to the drug and which disappeared as soon as the drug was stopped. The structural formula of ethyl vanillate might have suggested what already has been observed. Two cases on moderately high doses and with moderately high levels of the drug developed respiratory alkalosis and appeared to have a picture similar to that of salicylate poisoning. Several other infants had some degree of hyperpnea at some time during the course of treatment. Case 7 developed a high and perhaps toxic level (56 mg./100 cc.) early in his treatment. Autopsy findings showed necrosis of hepatic cells around the central veins and a degenerative change in the proximal convoluted renal tubules, lesions which are not seen in progressive histoplasmosis. It is possible that these were due to the drug and explain the failure in that case since the high and perhaps toxic level produced associated changes which would not allow the tissues to metabolize the drug to its effective end products or conjugates.

Discussion

Ethyl vanillate has, therefore, been used therapeutically on 12 cases of proved disseminated and progressive histoplasmosis at this writing. A study of the literature and the authors' experience with 23 previous cases falling into the category of progressive disseminated histoplasmosis have made it seem unnecessary to utilize control cases for such an evaluation. The patients reported would have been expected to die within weeks or months if some agent had not interrupted the usual course. Five of these infants and children are still alive and well following the use of ethyl vanillate in therapeutic doses for a reasonable period of time. These results are even more encouraging when one considers that most of the failures were too critically ill to expect improvement or were associated with factors which otherwise precluded adequate treatment.

As in other infections, the unknown factors, such as virulence of the organism, dose of the drug, and resistance of the host must be important in determining the course of the disease. Likewise, as in other infections, earlier diagnosis and earlier institution of therapy will undoubtedly improve the prognosis in all cases.

Conclusions

Ethyl vanillate is the only effective therapeutic agent for disseminated and progressive histoplasmosis which the authors have had an opportunity to try up to the present time. The margin between effective therapeutic levels and those which produce toxic manifestations is only about 25 to 30%, a margin of safety too small for a desirable therapeutic agent. However, in the case of progressive disseminated histoplasmosis we are dealing with an infection of such grave prognosis that one seems entirely justified in using any agent which offers some hope of therapeutic effectiveness and which does not regularly produce severe toxic manifestations.

Summary

Some of the physical and pharmacologic properties of ethyl vanillate, a new fungistatic or fungicidal agent, have been briefly stated.

The records of 12 patients with progressive disseminated histoplasmosis treated with ethyl vanillate have been reviewed. Five of these patients are alive and apparently well following treatment, an experience not previously encountered or reported in the literature.

The use of the drug in the treatment of histoplasmosis has been outlined and the toxic manifestations of overdosage have been described.

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Spanish Abstract

El Tratamiento de la Histoplasmosis Diseminada con "Ethyl Vanillate"

Se describen los propiedades físicas y farmacológicas de un nuevo agente fungicida o fungestático llamado "ethyl vanillate."

Los autores revisan las historias clínicas de doce pacientes con una histoplasmosis progresiva diseminada, tratados con "ethyl vanillate." De este grupo, cinco pacientes se encuentran vivos y en buen estado de salud despues del tratamiento con "ethyl vanillate." Reportes similares no se encuentran publicados en la literatura médica.

Los autores describen el uso de esta droga en el tratamiento de la histoplasmosis, asi como las manifestaciones tóxicas secundarias consecuencia de dosis excesivas.

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DIGESTION OF PROTEIN BY PREMATURE INFANTS

As Indicated by Nitrogen Absorption from Whole vs. Hydrolyzed Protein

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Boston

IT HAS been assumed from the early work of Gordon and Levine[1] that since premature infants have relatively high absorption coefficients for nitrogen, they therefore digest protein efficiently. The recent observations of Magnusson[2, 3] that such infants gain weight more rapidly when N is fed as amino acids instead of as whole protein have nevertheless suggested a relative impairment of protein digestion, especially during the first few weeks after premature birth. This indirect evidence of enzyme deficiency appeared to gain support from Werner's[4] histochemical studies on 42 premature and 19 full-term infants at autopsy. She demonstrated a marked paucity of pepsinogen and zymogen granules in the gastric mucosa and pancreas, respectively, of infants with birth weights below 2300 gm. as compared with larger and supposedly full-term infants. Since none of her subjects were more than 1 week old and most had died within 24 hours after birth, the evidence as to digestive inferiority would not apply to infants in the age range studied by Magnusson. Duodenal secretions obtained by Madey and Dancis[5] from 16 living premature infants from 2 to 23 days old were consistently normal in tryptic activity. Although these authors found no difference in weight gains of 16 premature infants fed equicaloric supplements of whole casein and of casein hydrolysate, it was considered of interest to repeat their investigation and to measure the absorption of N from whole and predigested dietary protein. Five premature infants were thus studied for periods varying from 2½ to 6 weeks.

METHODS

In all cases a standard mixture of evaporated milk, water and karo formed the basic formula and provided from 87.4 to 92.5% of calories. To this feeding, casein† or casein hydrolysate‡ were added in rotating periods, usually of 7 days. Appropriately large and constant amounts of ascorbic acid and other vitamins were administered to all infants in all periods. Stool collections were not begun until 2 days after each change of supplement to allow adjustment to the new feeding. The casein and hydrolysate additions were calculated to provide equal amounts of supplemental N. Quantitative changes in supplements and in basic formula were made only as needed to keep nitrogen intake in constant relation to body weight. Diet and fecal output were analyzed for N by standard macro-Kjeldahl technic. Since the question to be answered by this investigation concerned only the absorption of N from different sources, nitrogen retention was not determined.

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† Calcium caseinate (Casec), Mead Johnson and Company. (88% whole protein.)

‡ Enzymic hydrolysate (Protolysate), Mead Johnson and Company. (Total N = 65% free amino acids and 35% low molecular weight peptides; nitrogen content = 75% of that found in whole casein.)

Results

At the left of table 1 are shown the weight at birth of each infant and the weight and age at the start of the study. Columns 1, 2 and 3 indicate the calories/100 ml. of basic formula, of basic formula plus casein, and of basic formula plus casein hydrolysate, respectively. It will be seen that the calories in the hydrolysate supplemented mixture were slightly greater than in the casein supplemented one. This was necessitated by minor differences in the ratio of N to calories in the two supplements. From the remaining columns it will be noted that the additional N as protein or amino acids furnished at least 33% and, in Baby E, nearly 50% of the total fed. These substantial additions were

TABLE 1

				Calories			Nitrogen			
				(1)	(2)	(3)	(4)	(5)	(6)	(7)
Baby	Birth wt. kg.	Wt. at Start of Study kg.	Age at Start of Study Days	Basic Formula Cal./100 ml.	Basic Formula plus Casein Cal./100 ml.	Basic Formula plus Casein Hydroly-sate Cal./100 ml.	Basic Formula mg./100 ml.	Amount Added to Formula Casein or Hydroly-sate mg./100 ml.	Total mg./100 ml.	% total N from Supple-ment
A	1.870	1.984	13	52.5	56.8	57.4	320	160	480	33.3%
B	1.616	1.701	28	59.2	64.0	64.6	306	177	483	36.6
C	1.134	1.219	17	59.2	65.0	65.7	302	213	515	41.3
D	1.474	1.503	13	48.7	54.1	54.8	320	200	520	38.5
E	.907	.936	21	50.7	57.2	58.1	280	240	520	46.2

chosen in order to bring out even minor differences in absorption and, thus, in digestive powers.

Results are presented in table 2. The low caloric intake of Baby A was necessitated by a poor appetite for food, but it will be noted that the nitrogen content of the supplemented diets of all five infants (column 2) represented the equivalent of from 4 to 8 gm. protein/kg./day, and thus supplied a varied and rather high protein intake. It is obvious from column 5 that absorption was relatively similar on all types of feedings. The average daily weight gains in Infant A, B and C suggest a nutritional advantage for hydrolysates, though relatively short third periods in Infants A and B may have resulted in less than representative data. However, in Infants D and E, who received hydrolysates for the first period, no consistent superiority was observed for weight gain on either supplement.

Discussion

The supplements given these infants contained from 480-640 mg. N/kg./day. These amounts compare favorably with Magnusson's[2, 3] figures of approximately 400 mg. of supplemental N/kg./day.* However, since Magnusson's subjects received breast milk as their basic diet, their total nitrogen intakes were substantially less. The additional N offered to the infants studied by Madey and Dancis[5] was approximately 36% of the total

* 10 cc./kg./day of 25% amino acid solution or 2.5 gm. amino acids/kg./day.—$\frac{2500}{6.25} = 400$ mg.N./kg./day.

nitrogen intake while the total nitrogen content of their formula was 3.53%. These figures approximate closely those used in the present study, 33-46% and 3.10-3.25%, respectively.

Both Magnusson and Madey et al. studied their infants from birth through periods varying from 30 to 56 days and 40 to 50 days, respectively. In the present study the infants were from 13 to 28 days old at the start of the study and were followed for periods varying from 17 to 42 days. Thus, although circumstances in the three investigations were not strictly comparable, they were sufficiently similar to allow comparison of results.

TABLE 2

Infant	Period of Study	No. of Days	Form of Added Casein	(1)	(2)	Nitrogen (3)	(4)	(5)		(6)
				Caloric Intake Cal./kg./24 hr.	Protein Intake G./kg./24 hr.	Intake Mg./kg./24 hr.	Absorption Mg./kg./24 hr.	Coefficient of Absorption Absorption Intake	Mg./kg./24 hr.	Average Daily Wt. Gain gm.
A	1	5	Whole	91.8	4.27	684	592	.866		18
	2	5	Hydrolyzed	93.8	5.12	820	710	.866		28
	3	2	Whole	91.5	4.22	676	584	.864		7
B	1	5	Whole	150.8	6.78	1086	978	.901		28
	2	5	Hydrolyzed	138.2	6.52	1043	946	.906		45
	3	3	Whole	135.6	6.04	967	844	.873		43
C	1	5	Whole	159.8	7.64	1222	1120	.917		19
	2	5	Hydrolyzed	161.6	7.96	1275	1162	.912		39
	3	5	Whole	162.6	7.84	1255	1155	.920		34
	4	5	Hydrolyzed	154.0	7.70	1231	1141	.927		45
D	1	5	Hydrolyzed	131.0	8.16	1307	1202	.921		14
	2	5	Whole	134.6	8.05	1290	1173	.909		20
	3	5	Hydrolyzed	133.0	8.29	1327	1230	.927		28
	4	5	Whole	125.2	7.51	1201	1082	.900		34
E*	1	5	Hydrolyzed	142.2	8.49	1359	1283	.944		18
	2	5	Whole	143.6	8.04	1286	1176	.915		24
	3	5	Hydrolyzed	141.2	8.45	1352	1261	.934		34
	4	5	Whole	126.6	7.10	1136	1017	.896		34
	5	5	Hydrolyzed	127.4	7.58	1214	1098	.904		37
	6	4	Whole	133.7	7.60	1217	1134	.932		36

* Infant E received crude liver extract I.-M. every other day throughout the study; a transfusion of 23 ml. whole blood on the 3rd day of period 2, and transfusions of 28 and 20 ml. on the 2nd and 4th days, respectively, of period 3. No other treatment was given to any infant.

The present investigation showed a high degree of nitrogen absorption from both types of feedings. The inference is that the protein added as casein was efficiently digested, but the question of absorption of incompletely digested protein deserves consideration. It is generally assumed that no more than very minute amounts of whole protein may be absorbed from the gastrointestinal tract although traces must gain access to the blood stream to account for occasional allergic reactions.[6, 7] Only one piece of evidence as to absorption of intermediate digestive products has been found in the literature,[8] and this from animal rather than human material. In the dog unspecified amounts of polypeptides have been demonstrated in the mesenteric circulation from the small bowel. The question of significant absorption in human subjects thus remains open.

In the absence of the necessary information it can only be stated that even if digestion

is less than complete, absorption of the resultant partial breakdown products and their utilization for growth apparently occur.

The daily weight gains of infants in the present study were of the same order as those of infants reported by Madey and Dancis, but considerably less than those shown by certain of Magnusson's subjects during amino acid supplementation. He reported gains of 40 to 60 or more gm./day under those circumstances as against 25 gm. or less during casein supplementation. The basic diet used was breast milk. The low protein content of such a regimen might have produced circumstances more favorable to the effectiveness of supplemental predigested protein, though the mechanism is not clear. There remains the possibility that weight increases may have been affected by differences in mineral intake. Magnusson himself showed that this was not the explanation for superior weight gains by his patients. There are slight differences in mineral content of the supplements added in the present study, but since these would represent an excess of only about 80 mg./day for the hydrolysate supplement as compared to the casein, it is unlikely that this factor would significantly affect the rate of weight gain with either supplement.

Summary and Conclusions

Absorption of N from cow's milk mixtures supplemented with equal amounts of N as casein and casein hydrolysates was determined in 20 metabolic periods on five premature infants.

The supplemental protein or hydrolysate furnished from 33.3 to 46.2% of the nitrogen intake and total N fed was equivalent to 4.22 to 8.49 G. protein/kg. body weight. With either supplement from 86 to 94% of the dietary N was absorbed and neither resulted in consistently superior nitrogen absorption.

Weight gains were not consistently better during either type of supplemental feeding.

The evidence of equally satisfactory nitrogen absorption and weight gain would substantiate the prevailing belief that protein digestion is not impaired after premature birth.

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SPANISH ABSTRACT

La Digestión de Proteínas por Prematuros Medida por la Absorción de Nitrógeno Derivado de la Ingestión de Proteína Total o de Proteína Hidrolizada

La absorción de nitrógeno derivada de mezclas de leche de vaca suplementada con cantidades iguales de nitrógeno en forma de caseína o caseína hidrolizada, fué determinada en veinte períodos metabólicos en cinco prematuros. Este suplemento de proteína representó de un 33.3% a un 46.2% de la ingestión de nitrógeno y el total de nitrógeno ingerido representó de 4.22 a 8.49 gramos de proteína por kilogramo de peso. Con ambos suplementes se obtuvo una absorción del 86% al 94% del nitrógeno de la dieta. Con ninguno de estos dos suplementos se obtuvo siempre una mayor absorción de nitrógeno que con el otro. Tampoco se obtuvo siempre un mayor aumento de peso con un suplemento que con el otro. Estos dos hechos corroboran la creencia prevaleciente de que la digestión de las proteínas no se ve afectada por un parto prematuro.

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SMALLPOX VACCINATION WITH PROLONGED VACCINIA

By JOHN A. BIGLER, M.D., AND EUGENE L. SLOTKOWSKI, M.D.
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THE interest in the case reported in this paper lies in the fact that, in addition to the severity of the primary vaccination take, vaccinia lesions continued to appear over a four month period until death occurred. There are reports in the literature of extremely severe primary vaccination reactions with and without death. Cases of xeroderma pigmentosum (Kaposi's disease) and vaccinia vaccinatum have also been reported frequently; in these, death occurred or the disease ran a self-limited course with all lesions in the same stage. The authors have been unable to find reports in the literature in which the vaccinia lesions continued to appear after the original vaccinia should have run its course.

CASE REPORT

O. W., a Negro female, was admitted to the Children's Memorial Hospital at 5½ yr. of age and died 3 mo. later. Family history and early development were unknown as she was an adopted child. Birth weight was 2.3 kg. and the birth was that of a normal spontaneous delivery.

Past History: She was immunized against diphtheria and tetanus during infancy. A smallpox vaccination during this period did not take. There was a history of pertussis 1 yr. prior to admission. There was no history of eczema.

Six weeks before admission, there was exposure to rubeola. Three days later both a diphtheria booster injection and a smallpox vaccination were given. It could not be established that these were done on the same arm. One week later rubeola developed and was complicated by a bronchopneumonia. During this period she received 3 daily injections of penicillin until the pneumonia cleared. The penicillin preparation given is unknown and presumably it was given in the buttocks. During the time she had the pneumonia, the vaccination took as a primary take. This was covered with a celluloid shield. Fever continued, the site of the vaccination continued to enlarge and there was pain, swelling and tenderness of the left arm. She was admitted to The Children's Memorial Hospital 5 wk. after the vaccination.

Physical Examination: The patient was a small, slender, moderately well-nourished, acutely ill, Negro female about 5 yr. of age and weighing about 15.9 kg. The skin was hot and she guarded her left arm. The temperature was 38.5°C., the pulse 120 and respirations 24. The eyes, ears and nose were normal. Over the tongue, buccal mucous membranes and hard palate were multiple small, white, foul-smelling plaques—some of which could be wiped off without leaving a bleeding surface. The neck, chest and lungs were normal. The heart was normal except for a functional systolic murmer at the base. The abdomen, genitalia and extremities were normal except for the left arm. Over the deltoid region of the left arm there was a necrotic area measuring about 7 by 7 cm. The border was raised and there was a terraced arrangement with a greyish color. The center was a large, blackish, necrotic dry crust. On the edges of the ulcer and surrounding it were 8 to 10 vesiculopustular umbilicated lesions, 1 to 2 cm. in diameter with a dry, grey, central crust. The shoulder, arm and hand were swollen about half again normal size. The upper arm and shoulder were a reddish blue, markedly tender and there was a firm, brawny induration. In the axilla there was a moderate, firm adenitis. The radial pulse was normal. No eczema was present.

Progress: There was a daily elevation of temperature from 37.8° to 38.3° up to 39.4° to 40.0° C. during the entire course of the disease. There was a steady loss of weight and increasing

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toxicity. The lesions in the mouth never healed and the one on the palate became necrotic. The shoulder, left arm and hand became about twice normal size. The ulcerated lesion of the upper arm increased in size so that it extended about three-fourths of the way around the arm (Fig. 1). The radial pulse was obtainable at all times.

A paronychia developed on the right middle finger on the 16th hospital day and was opened 1 wk. later. Eleven days later, new vesiculopustular, umbilicated, crusted lesions began to appear on the left shoulder and back (Fig. 2). Eight days later similar lesions appeared on the face and the right index finger. These lesions were all in areas that could be contact infections. Three months after

FIG. 1. Left arm and shoulder 8 days after admission and approximately 6 wk. after vaccination. Vesiculo-pustular lesions surround necrotic area.

admission, a new lesion appeared on the right wrist. All these lesions became necrotic and were active and present at death. At no time was there evidence clinically of an encephalitis.

Laboratory Examinations: Hgb. was 11 gm./100 cc., RBC 3.8 to 4.0 million/cmm. and WBC 15.3 thousand/cmm. with 90% polymorphonuclears, 4% lymphocytes, 4% monocytes and 2% eosinophils. The urine was negative except for 2 occasions during sulfonamide therapy when albumin and red cells were present. This cleared promptly after discontinuing the sulfonamides. Blood serology and the Mantoux test were negative. Nose and throat cultures were negative for diphtheria bacilli, but there was a slight growth of Staph. albus, Str. viridans and diphtheroid bacilli. Blood cultures were consistently negative.

On culture from the surface of the lesions there were growths of Staph. albus, Str. viridans and B. pyocyaneus. A salmonella was reported once. Pus from deeper in the lesions was negative on culture. Dark field examination of scrapings of the lesions was negative.

Roentgenograms of the heart and lungs were normal. Films taken of the left arm on 3 occasions were normal.

Therapy: Many forms of both local and general therapy were used in various combinations. Locally, the large necrotic area was surgically cleansed and debris removed. Locally, at different intervals, potassium permanganate soaks, tyrothricin (1½ cc. to 100 cc. water) dressings, zinc peroxide dressings and 2% gentian violet were used. Penicillin, 50,000 units, and streptomycin, 125,000 units, were given intramuscularly every 3 hr. Ascorbic acid, 100 mg. twice daily, and 5 drops of a saturated solution of potassium iodide were also given. Sulfadiazine, 0.5 gm., was given orally 5 times daily in combination with the penicillin for an interval. During all forms of therapy there was a steady advance of the lesions and deterioration of the patient's condition.

FIG. 2. Left arm and shoulder approximately 15 wk. after vaccination. Except for digits of hand, entire upper extremity has been involved. New vesiculo-pustular, umbilicated lesions are noted on left shoulder and neck.

PATHOLOGY

At the time of autopsy a virulent organism of some type was suspected as the causative agent of the necrotic lesions. Special precautions were observed in order to prevent the spread of any tissue or body fluids. The individual organs were not weighed. The body was that of a poorly-nourished, emaciated, Negro female with pustular and ulcero-gangrenous lesions involving the face, trunk and upper extremities (Figs. 3, 4 and 5). A fairly well circumscribed, 25 to 30 mm. in diameter, rounded, ulcero-pustular lesion with an elevated rounded border and a depressed, necrotic crusted center was present to the right of the nasal bridge and just below the inner canthus of the eye (Fig. 5). The left upper extremity was ulcerated, necrotic, gangrenous and discolored (Figs. 3, 4 and 5). The skin had been completely eroded by the necrotizing process and the entire upper extremity from the shoulder to the finger tips was increased in size, bluish-black in color and hard in consistency. The surface was uneven and irregular. Muscle tissue as such could not be identified. The involved area contained a considerable amount of cellular debris. At no point on

the left upper extremity could normal epidermis be identified. The necrotic lesion included portions of the shoulder and trunk, almost reaching the midline anteriorly and extending over the scapular area posteriorly. The tissue at the point of junction between the necrotic lesion and the relatively normal skin was swollen, soft and friable. Circumscribed circular lesions, measuring up to 15 mm. in diameter with elevated borders and depressed, necrotic centers, were present along the periphery of this huge ulcer. The ulcer had partially eroded

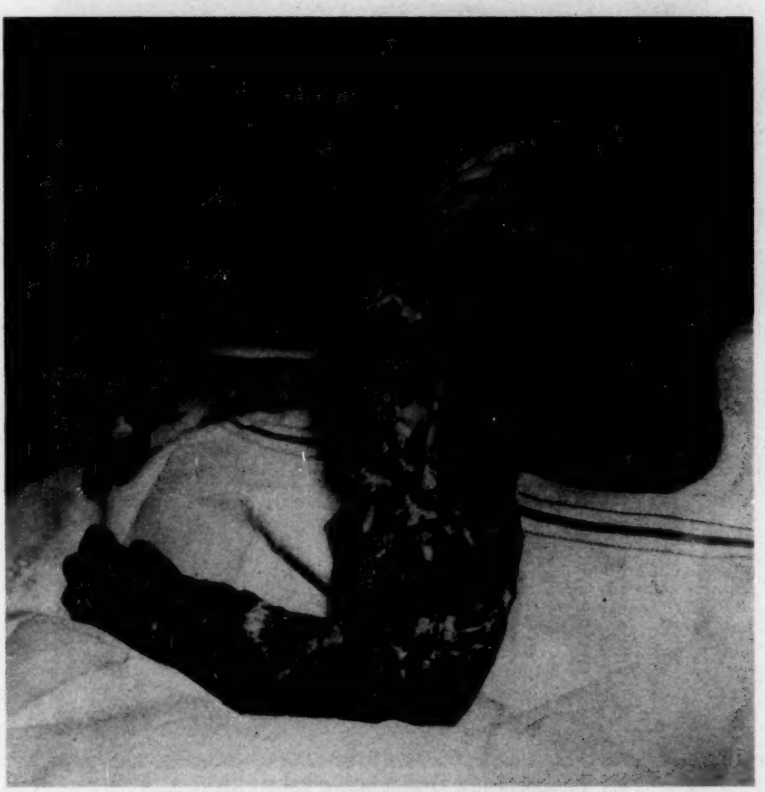

FIG. 3. Patient 4 mo. after vaccination and shortly before death. Digits of right hand, except for little finger, are involved by eroding, necrotizing process.

into the smaller lesions, giving its margin a scalloped appearance. The skin of the trunk posteriorly was reddish-purple in color and was covered with deeply-pigmented, coarse scales and pustules which were from 3 to 5 mm. in diameter (Fig. 4). In addition, four large ulcero-gangrenous lesions measuring 3 to 5 cm. in diameter with elevated borders and depressed, necrotic centers were found. A sharply circumscribed decubitus ulcer measuring 4 cm. in diameter was present over the left buttock. It extended through the adipose tissue down to the muscle mass. Involvement of the right upper extremity was limited to the digits and the wrist. The thumb, index, middle and ring fingers were ulcerated, necrotic and brownish-red in color; the skin had been completely destroyed. On the ex-

tensor aspect of the right wrist there was a well-circumscribed, rounded lesion measuring 1 cm. in diameter with an elevated border and a depressed, crust-covered center. The lesions on the wrist and the nose and the satellite-like lesions along the periphery of the huge ulcer in many respects resembled lesions of a primary vaccination.

The abdominal cavity did not contain any free fluid. The liver edge extended four fingerbreadths below the costal margin. It was enlarged, pale and flabby. Grossly and on

FIG. 4. Posterior view of trunk shortly before patient's death.

cut section the surface was studded with many brownish-red areas measuring 1 to 2 mm. in diameter which stood out against the pale, yellowish-brown background.

Approximately 10 cc. of a clear, straw-colored fluid was present in each pleural cavity. Fine fibrinous adhesions were present between the right surface of the right upper lobe anteriorly and laterally and the adjacent thoracic cage. The upper lobes of both lungs were pale and crepitant. The lower lobes were purplish-blue in color and firm in consistency. On cut section, especially in the lower lobes, the parenchyma was moist and discolored and the sections sank immediately in the formalin solution. The trachea and bronchi were filled with a bubbling, frothy, mucoid material.

Except for a decrease in the size of the thymus, vascular congestion and cloudy swelling, the changes in the other organs were not unusual.

Microscopic examination of the skin revealed a complete loss of cutaneous epithelium in sections taken from the center of the huge necrotic lesion. This area contained amorphous, pale, basophilic material as well as many mononuclear cells. Sections taken through the border of the necrotic lesion from the left shoulder and right wrist revealed a variety of pathology. The greatest changes were found in the cells of the malpighian layer. The cells were swollen; the cytoplasm had lost its normal character and stained very faintly.

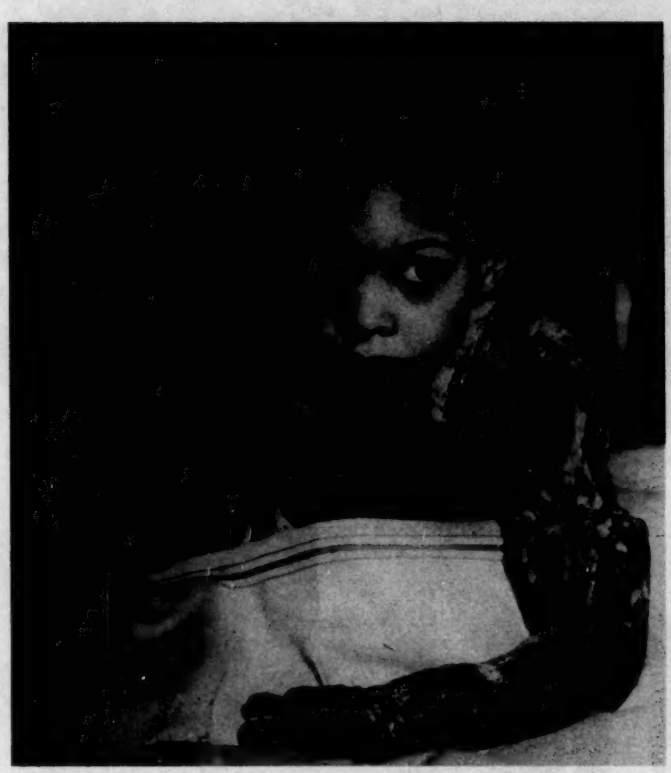

FIG. 5. Patient shortly before death. Note fairly well circumscribed, umbilicated, crusted lesion on face just below inner canthus of right eye.

This gave the nucleus a halo-like appearance (Fig. 6). Many of the nuclei had lost their form, appeared shriveled, were irregular and had assumed peculiar shapes. Some were flattened and displaced toward the cell periphery. Where the cytoplasm appeared to have undergone liquefaction, the vacuoles were separated by strands of tissue which probably represented the cell membranes. This presented a lattice-like network. Large multi-locular vesicles had formed where the cell membranes had been destroyed (Fig. 7). The roof of the large vesicles was composed of a horny layer, while the side and base were limited by cells undergoing various stages of swelling and degeneration. Faintly stained, rounded structures were noted in the swollen cytoplasm. These were believed to be Guarnieri's bodies—swollen nucleoli which had escaped from the nucleus into the cell plasma (Fig. 8).

Microscopic examination of the lungs revealed many alveolar spaces which were com-

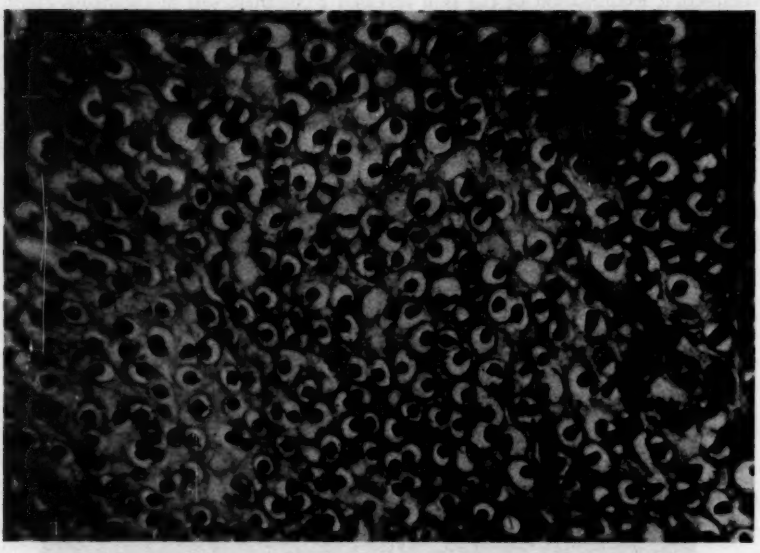

FIG. 6. Photomicrograph (high power) of skin at margin of necrotic lesion. Cells are swollen, cytoplasm has lost its normal character and stains very faintly.

FIG. 7. Photomicrograph (medium power) of skin showing swollen cells, faintness of cytoplasm and formation of large vesicle where cell membranes have been destroyed.

pletely filled with polymorphonuclear leukocytes, indicating an extensive bronchopneumonic process. Many of the polynuclear cells were in various stages of degeneration. In these areas the landmarks were markedly distorted and lung tissue was identified with difficulty. Other alveoli contained clear, homogenous fluid or many red blood cells. The mucosal lining of the smaller bronchi and that of many bronchioles was either completely absent or only small segments were identified. In many areas the bronchial and bronchiolar mucosal lining had undergone metaplastic changes. Some of the alveolar spaces were either

FIG. 8. Oil immersion photomicrograph showing presence of Guarnieri's bodies in cell cytoplasm.

partially or completely filled by closely grouped septal cells. Many large, basophilic, multinucleated giant cells were found throughout the lung parenchyma.

The changes in the other organs of the body were nonspecific in nature.

DISCUSSION

At the time of autopsy three possibilities were considered as being the cause of death: first, the vaccination site acted as a portal of entry for some infectious agent—fungus, bacterial or viral—the part played by the vaccination being purely incidental and circumstantial, allowing the infectious agent to invade the tissues. Second, contamination of the vaccination site by some infectious agent plus a superimposed change in the permeability of the tissues, the so-called Duran-Reynals' phenomenon.[1] Third, the necrotic lesions and the death were directly attributable to the vaccination—for some unknown reason the patient having reacted atypically to the introduction of the vaccinia virus.

The first possibility was ruled out fairly well by the fact that all aerobic and anaerobic cultures grew bacteria and yeasts which were considered contaminants. This was not unusual in view of the extensive necrotic areas. In addition, the patient failed to respond to various forms of local and systemic therapy. The second possibility, that a Duran-Reynals' phenomenon played a part in the spread of the lesion, could not be ruled out.

However, the involved areas never assumed the violent inflammatory status which would be expected if a spreading factor complicated the vaccinial lesion. The lesions spread continually but rather slowly. The third possibility, that the death of the patient was directly attributable to the vaccination, was borne out by microscopic examination. Sections of skin immediately adjacent to the necrotic areas revealed changes which were identical to those expected during the vesiculo-pustular stage of a primary vaccination take.

In order to understand the pathogenesis in this atypical case, it might be worth while to review the clinical, immunologic and histologic changes in a patient with a primary vaccination reaction. As a rule the course is quite uniform. After implantation of the vaccinia virus the lesion passes through the typical stages, reaching its full development on the ninth or tenth day, followed by drying, crusting and scarring. Immunologically, there is a definite time relationship between the introduction of the vaccinia virus and the appearance of specific antibodies in the blood. Blattner, Heys and Gollub[2] report that humoral antibodies to vaccinia begin to appear at the end of the first week following cutaneous vaccination, increase in amount during the second and third weeks and reach a maximum at the end of the third week. Blattner[3] also has had a case in a child that developed impetiginous lesions (question of vaccinia) after a smallpox vaccination. In material from these lesions, taken 15 days following vaccination, vaccinia lesions were demonstrated. This child did not show a significant rise in blood titer until five weeks following vaccination.

Microscopically, the changes in vaccinia are identical to those in variola. This is not surprising since vaccinia and variola are believed to be due to the same virus. When variola is inoculated into cattle and carried through several transfers in these animals, the virus (variola) becomes attenuated and approaches the nature of vaccinia.[4] Changes in the malpighian layer of the epidermis consist of swelling, cytoplasmic degeneration and liquefaction, formation of multilocular vesicles and the presence of Guarnieri's bodies. Guarnieri's bodies are swollen nucleoli which have migrated from the nucleus into the cytoplasm. The primary necrosis in the vaccinia lesion is believed to be due to the direct action of the virus on the epithelial cells.

These microscopic changes were present in the sections of the skin taken at the time of autopsy in this case. Sections were mailed to Dr. Ernest W. Goodpasture, Vanderbilt University, who expressed the opinion that the lesions were caused by a virus and all the evidence indicated that the particular virus concerned was a strain of vaccinia and that it was difficult to explain this situation except on the inability of the child to develop immunity.

Summary

Definite clinical, histologic and immunologic changes take place following smallpox vaccination. After its full development on the ninth or tenth day, the vaccinial lesion is followed by drying, crusting and scarring. Histologically, there are degenerative and irritative changes in the epidermis believed to be due to the direct action of the virus on the epithelial cells. Immunologically, humoral antibodies to vaccinia begin to appear at the end of the first week following cutaneous vaccination, increase in amount during the second and third weeks and reach a maximum at the end of the third week. The probable reason for the involution of the vaccinial lesion after the pustular stage is the appearance of specific antibodies in the blood which apparently neutralize the vaccinia virus. The presence of histologically active vaccinial lesions approximately four months after

implantation of the vaccinia virus could only be explained on the inability of the child to develop immunity to the vaccinia virus. Because of this lack of immunity, degenerative action of the vaccinia virus continued unopposed.

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Spanish Abstract

Vacunacion Antivariolica Seguida de Vaccinia Prolongada

Cambios clínicos, histológicos e inmunológicos ocurren en la vacunación contra la viruela. Después del desarrollo completo de la reacción en el noveno o décimo día, las lesiones vaccinales se secan, forman costra y cicatrizan.

Histológicamente, ocurren cambios degenerativos y irritativos en la epidermis, posiblemente debidos a la acción directa del virus sobre las celulas epiteliales. Inmunológicamente, los anticuerpos humorales contra la vacuna comienzan a aparecer al final de la primera semana siguiente a la vacunación, aumentando progresivamente durante la segunda y tercera semana para alcanzar un nivel máximo al final de la tercera semana. La cause probable de la involución de la lesión vaccinal después de la fase pustular, es la aparición en la sangre de anticuerpos especificos que neutralizan el virus. La persistencia de lesiones vaccinales histológicamentes activas, aproximadamente cuatro meses después de la inoculación del virus, puede explicarse solamente por la imposibilidad del paciente en desarrollar suficiente inmunidad contra el virus de la vacuna. Consiguientemente, la acción degenerativa del virus de la vacuna continúa actuando sin oposición.

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SUBDURAL EFFUSIONS COMPLICATING BACTERIAL MENINGITIS

By MARGARET H. D. SMITH, M.D., RICHARD E. DORMONT, M.D., AND GEORGE W. PRATHER, M.D.

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POTENT chemotherapeutic agents have greatly increased the survival rate in all types of acute bacterial meningitis. Even infants with meningitis due to pneumococcus and H. influenzae can be expected to survive in 60 to 90% of all cases, according to recent experience.[1, 2] Unfortunately, an appreciable number of the survivors suffer from permanent brain damage of one sort or another.[2, 3] Recently Crook, Clanton and Hodes,[2] in a careful study of 64 patients recovered from influenzal meningitis, found that 12 of these had apparent brain injury attributable to their meningeal infection, while the 52 patients without gross apparent brain damage showed a lower average intelligence than that of the pediatric population at large. It behooves us therefore to seek ways of shortening the period of active infection, in the hopes of lessening the damage done by increased intracranial pressure and by impaired cerebral circulation.

One cause for sequelae from meningitis which has been overlooked until recently[4] is the frequent occurrence of subdural collections of fluid. Some data on the incidence, etiology and clinical manifestations, together with a brief discussion on pathogenesis and therapy of these effusions, will be presented.

CLINICAL FEATURES

I. Incidence of Subdural Effusions.—During an 11 month period 43 patients under the age of 2 years were admitted to the Pediatric Services of the Charity Hospital because of bacterial meningitis. This figure includes all the patients under the age of 2 years in whom the etiologic agent of meningitis was established beyond doubt by isolating the agent from the spinal fluid at the time of admission. The cases of tuberculous meningitis and also a few cases where the diagnosis remained in doubt are not included here. Of this number, 17 patients had meningitis due to H. influenzae, 16 to D. pneumoniae, 7 to N. meningitidis, one each to Ps. aeruginosa, Salmonella sp. and paracolon bacillus. Subdural effusion was demonstrated in exactly 20 of these patients, that is, in almost half of all the infants with meningitis. In most of the others, subdural taps were not performed, so that the figure for the incidence almost certainly errs on the side of being too low.

II. Age of Patients with Subdural Effusions.—The age incidence of subdural effusions in this series corresponds roughly with the expected age incidence of bacterial meningitis, being highest between the ages of 3 and 9 months[5, 6] (see chart 1). It must be pointed out, however, that the patients in whom the subdural taps were performed were those with open fontanelles; it is not known how often subdural fluid might be found in older patients.

III. Etiology and Treatment of the Underlying Meningitis.—Subdural effusions were

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present in patients with several different kinds of meningitis. H. influenzae type b was responsible for the underlying meningitis in 9 patients, D. pneumoniae in 8, paracolon bacillus and Ps. aeruginosa in one each. In one patient both H. influenzae and D. pneumoniae were cultured from the spinal fluid. Surprisingly enough, two infants under treatment for tuberculous meningitis have shown no subdural effusions, despite the fact that such an association was reported many years ago.[7] The present authors have had too few cases of meningococcic meningitis recently to know whether these patients develop

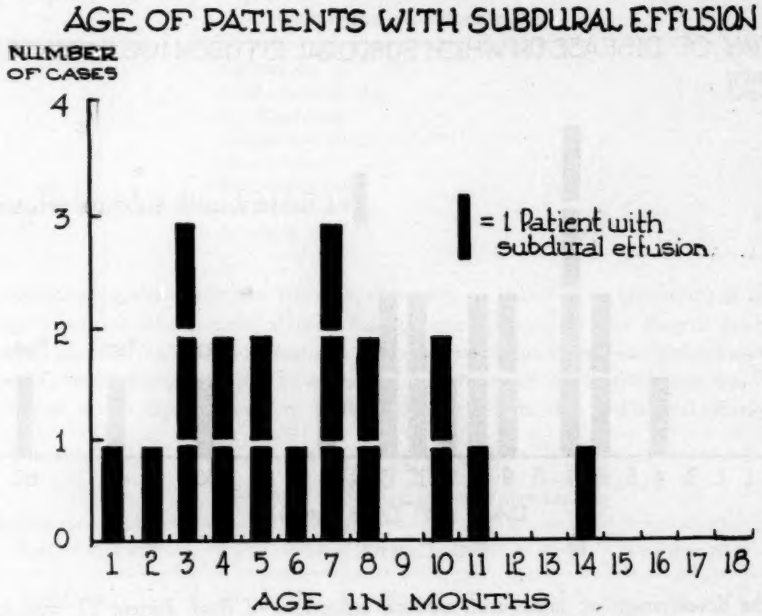
AGE OF PATIENTS WITH SUBDURAL EFFUSION
NUMBER OF CASES
4
3
2
1
0
= 1 Patient with subdural effusion
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN MONTHS

CHART 1.

similar effusions. Presumably some of them do if the disease is present for some time before the patient comes under treatment. Schwartz reports such a patient from his own experience.[8]*

As to the severity of meningitis, 17 of the 20 patients might be classified as severely ill or "moderately severely ill" on admission; 3 were only mildly ill.

The manner in which the meningitis was treated varied greatly from case to case, depending on etiology and on many other factors. Combinations of the following therapeutic agents had been used prior to discovery of the subdural effusion: penicillin, streptomycin, chloramphenicol, sulfadiazine and rabbit antibody specific for H. influenzae type b. In the one patient with Pseudomonas meningitis, sulfabenzamine and aureomycin also

* Since writing this paper, the authors have admitted an 11 month old white male with meningococcal meningitis of 3 days' duration. Though treated with sulfadiazine, penicillin and chloramphenicol, fever and irritability persisted. On the 13th day of illness a subdural effusion of 7 cc. of clear fluid was found on the right side. No fluid was present on the left side. The effusion had cleared by the 4th tap, done on the 21st day of illness.

were employed. None of the patients in this series had received any intrathecal medication prior to the recognition of the subdural fluid.

IV. Day of Disease on Which Subdural Effusion Was Discovered.—Most of the subdural effusions were discovered during the second week after onset of symptoms of meningitis. By that time the patient had been admitted to the hospital and had had what in most cases would constitute adequate chemotherapy (chart 2).

In 15 of the 20 patients fluid was obtained at the time of the first subdural tap. This militates against the idea that trauma incident to subdural taps was in any way responsible

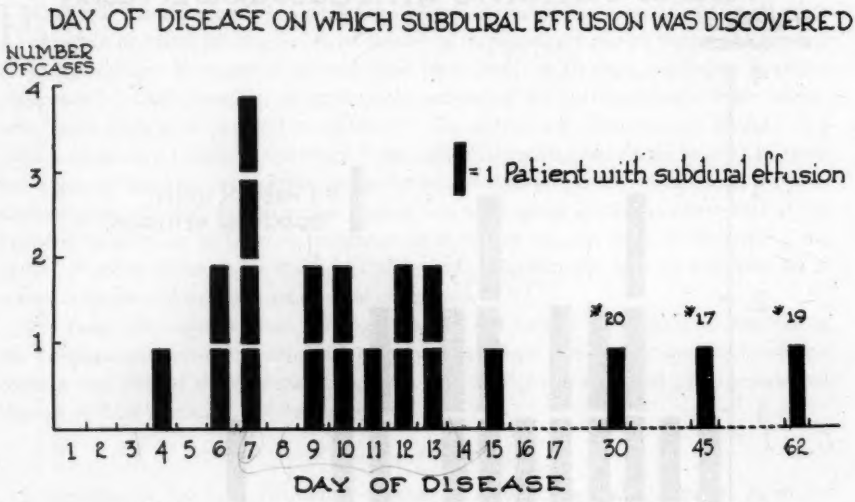
DAY OF DISEASE ON WHICH SUBDURAL EFFUSION WAS DISCOVERED
NUMBER OF CASES
4
3
2
1
= 1 Patient with subdural effusion
*20
*17
*19
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 30 45 62
DAY OF DISEASE

CHART 2.

for the development of subsequent subdural collections of fluid. Patient 17, who had influenzal meningitis, had been treated elsewhere for pneumonia for 45 days before being brought to Charity Hospital. At the time of admission his head was definitely enlarged, and subdural taps were positive. In Patient 20, who was suffering from paracolon meningitis, subdural taps were performed seven times between the third and thirtieth day, before fluid was obtained. In Patient 19, subdural taps performed at intervals after the fifteenth day yielded fluid only at the ninth attempt (sixty-second day of the disease).

V. Indications for Subdural Taps.—In recent months subdural taps have been performed once or twice as a routine measure in all infants recovering from meningitis. Nine of the effusions reported here were discovered on "routine" tap. In the remaining 11 patients one or more indications for tap were present, such as convulsions and focal neurologic signs, persistent fever, chronic meningitis, opisthotonus, bulging fontanelle, projectile vomiting and enlarging head (see table 1).

VI. Characteristics of the Subdural Fluid.—

A. Appearance: the fluid obtained at the first tap was variously described as "xanthochromic," "bloody," "blood-tinged," "deep orange" or "purulent." Most often it was xanthochromic as long as any could be obtained on tap, in others it became less yellow or even clear.

B. Amount: Taps were performed in each patient at the start at the two lateral angles of the anterior fontanelle. In some, where fluid was found in the beginning only on one side, subsequent taps were performed only at the site where the fluid previously had been demonstrated. Considering only the first positive tap in each patient, fluid was found to be present bilaterally in amounts of 1 cc. or more in 11 patients, on one side only in 8 patients. (One patient is here omitted from consideration because, although 75 cc. were

TABLE 1

INDICATIONS FOR SUBDURAL TAP

Convulsions Focal neurologic signs	7
Persistent fever	3
Chronic meningitis	2
Opisthotonus	2
Bulging fontanelle	2
Projectile vomiting	2
Enlarging head	1

withdrawn initially from the left side, there was no record of a right subdural tap.) Of the 8 patients who initially showed fluid on one side only, 4 later showed fluid on the other side also. In 2 of the remaining 4 the apparently unaffected side yielded no fluid on at least one subsequent tap. The amount of fluid obtained at any given time was variable. A total of 111 taps yielded 2 cc. of fluid or more (in the case of bilateral effusions each

TABLE 2

AMOUNT OF FLUID OBTAINED ON SUBDURAL TAP

Amt. of fluid in cc.	2–5	6–10	11–20	21–30	31–60	More than 60	Total
No. of taps	30	43	20	6	3	9	111

tap from each side was counted separately). The distribution of the amounts present is shown in table 2.

C. Protein and Sugar Content: The protein content was determined quantitatively on 59 specimens of fluid, and varied between 40 and 1920 mg./100 cc. Most often it lay between 50 and 1000 mg./100 cc., and was always strikingly higher than the protein content of the spinal fluid determined simultaneously. In a number of patients there seemed to be a tendency for the protein content of the fluid to rise as time went on.

Glucose was determined quantitatively on 50 specimens of subdural fluid, and was found to be between 33 and 184 mg./100 cc., with the exception of one patient in whom the fluid was cloudy and showed a sugar content of 24 mg./100 cc.; this fluid was not cultured. In general, the glucose content of the subdural fluid was higher than that of the spinal fluid.

Similar findings have been reported by others with respect to protein and glucose content of subdural effusions.[4, 9]

D. Bacterial cultures: The subdural fluid was cultured in most cases, at least at the time of the first tap. In three patients the culture of the subdural fluid was positive, yield-

ing twice H. influenzae type b, once a paracolon bacillus. In one patient H. influenzae type b was recovered from the subdural fluid despite a negative spinal fluid smear and culture. The authors have recently had a similar experience in a patient admitted subsequent to the group of patients reported here. In both cases the positive subdural fluid culture made it possible to identify with considerable certainty the etiology of the antecedent meningitis and to institute rational treatment. The authors believe it important to perform subdural taps routinely in the case of infants treated elsewhere for meningitis before admission to Charity Hospital.

One patient was particularly noteworthy: this 3 month old white male infant was treated for meningococcal meningitis at another hospital for seven days. At the time of discharge he was said to have been unusually irritable. Four days later, fever and right-sided convulsions appeared. During the next 24 hours two more convulsive episodes occurred, the final one spreading to involve the left arm. Transferred to this hospital at this time, he was found to have a temperature of 37.8°C., a bulging fontanelle, a rigid spine, positive Kernig and Brudzinski signs, and a contralateral leg sign. The spinal fluid on admission showed a pressure of 240 mm., 400 cells of which 75% were polymorphonuclears; protein, 202 mg./100 cc.; glucose, 45 mg./100 cc., and a negative smear and culture. He was treated with penicillin, streptomycin, and sulfadiazine for meningitis of unknown etiology. On the fifth day after therapy was stopped, culture from a sixth subdural tap on the right was positive for H. influenzae type b. This cleared following administration of chloramphenicol.[10] Subsequent culture of the subdural fluid was negative.

VII. Management of the Subdural Effusions.—In all but one of these patients subdural taps were carried out repeatedly, either until no further fluid could be obtained, or until the fluid had decreased to very small amounts, and the patient seemed clinically improved.

The question arose as to the amount of fluid which could safely be removed at one time from the subdural space. In general the plan was to drain off the fluid until the free flow had stopped. Amounts as large as 60 to 75 cc. were removed on several occasions from one side without causing any apparent untoward reaction, despite the observations of Naffziger and Brown[11] and the misgivings expressed by Ingraham and Matson.[9]

Two patients were operated upon; their histories were as follows:

R. A., a 6 mo. old white male, was admitted because of high fever of 12 days' duration. For 3 days prior to admission projectile vomiting and right-sided convulsions had been present. Penicillin and sulfadiazine had been given intermittently from the onset of illness until admission. Physical examination revealed a severely ill, lethargic infant with a temperature of 37.2°C., a bulging fontanelle, stiff neck and hyperactive deep reflexes. The right pupil reacted poorly to light, there was ptosis of the right upper lid and right-sided weakness. The spinal fluid on admission showed 220 cells, glucose 60 mg./100 cc. and no organisms on smear; culture yielded H. influenzae type b. The patient was then given chloramphenicol 250 mg. every 8 hr. for 14 days and a total of 150 mg. of H. influenzae type b antiserum.

Although the temperature became normal 4 days after chloramphenicol was started, the patient continued to have projectile vomiting, right-sided convulsions and right-sided weakness. A subdural tap at this time yielded 20 cc. of xanthochromic fluid from the left and 1 cc. from the right side. The left subdural fluid contained numerous red blood cells, protein 648 mg./100 cc. and glucose 92 mg., but the culture was negative. Five subdural taps were then done over a 9 day period; large collections of fluid were obtained repeatedly from both sides. In order to investigate the nature of the residual pathologic lesion, bilateral trephination was done 39 days after the last subdural tap. The arachnoid was found to be markedly thickened and opaque. No membrane or hematoma was found. The postoperative course was uneventful and the patient appeared well at the time of discharge.

D. L., a 14 mo. old white male, was admitted because of fever and vomiting of 7 days' duration. One day prior to admission he had a right-sided clonic convulsion and became lethargic.

Physical examination on admission revealed a lethargic, severely ill infant with a temperature of 39.4°C., bulging fontanelle, stiff neck and hyperactive deep reflexes. Gram-negative pleomorphic organisms which quelled with H. influenzae type b antiserum were demonstrated upon examination of the admission spinal fluid. Subdural taps were negative on admission.

The patient was treated with chloramphenicol 250 mg. every 8 hr. for 10 days and a total of 175 mg. H. influenzae type b antiserum. The temperature became normal on the sixth day of therapy and the spinal fluid clear of cells. However, because of persistent vomiting and a bulging anterior fontanelle, subdural taps were repeated on the eighth hospital day and yielded 12 cc. of xanthochromic fluid on the right side and 10 cc. on the left side. The protein content of this fluid was 544 mg./100 cc., glucose 46 mg./100 cc., and cultures were negative. Spinal fluid drawn at the same time contained protein 67 mg./100 cc. and glucose 57 mg./100 cc. The vomiting was relieved by the subdural tap. Because of persistent high protein levels (up to 1920 mg./100 cc.) and repeated large collections of fluid on subsequent subdural taps, craniotomy was done on the left side. Upon excision of the dura a purplish membrane was exposed, which contained 90 cc. of xanthochromic fluid. In contact with the hemisphere forming the deep wall of this sac, another membrane was found. A large portion of both membranes was removed. Pathologic examination of both membranes showed them to consist of granulation tissue with chronic inflammation and hemorrhage.

Following craniotomy the patient had a stormy course with high fever; he developed osteomyelitis of the bone flap, which had to be removed surgically. All cultures of the purulent exudate were negative; following removal of the infected bone flap, the patient recovered completely.

Discussion

How Much Fluid is Normally Present in the Subdural Space?—In 1924, Penfield, having had occasion to observe a child with subdural effusion secondary to intracranial infection,[12] sought an answer to this question. In the course of ingenious experiments,[13] he was able to show that considerable variation in the amount of subdural fluid exists even in normal animals. The total amount of fluid varied from 1 to 2 drops to about 1 cc. in a dog weighing 5 kg. It was difficult in some dogs to demonstrate any fluid at all over the cerebellar arachnoid and none was demonstrable beneath the spinal dura over the cervical cord. He found the normal subdural fluid to be more yellow than the arachnoid fluid, showing that it does not take part in the cerebrospinal fluid circulation. Penfield concluded that the subdural space was actually more than a potential cavity in normal dogs.

Wycis[14] in 1945 mentioned seeing subdural fluid well up out of the subdural space when the subtemporal dura was nicked during operations on the gasserian ganglion, but he went on to say that estimates of the normal amount of fluid in the subdural space have not been made in humans, many neurosurgeons feeling that no subdural fluid is normally present.

Ingraham and Matson,[9] with their wide experience, state that "under normal conditions a few drops to 1 cc. of clear colorless fluid with a low total protein content may be obtained from the subdural or subarachnoid space."

Historical Review: Collections of subdural fluid, often referred to as subdural hydromas or hygromas, sometimes as subdural effusions, meningitis serosa traumatica, arachnoiditis, etc., have been observed for many years. Up to the present time the majority of subdural hydromas reported have occurred following head injury. The opinion that they may sometimes be due to other causes was, however, expressed by several authors early in the present century. Schwartz[8] in 1916, discussing the experience of his contemporary clinicians with respect to pachymeningitis, expressed the opinion that "a primary serous subdural exudation occurred in pachymeningitis," and again that "pachymeningitis and leptomeningitis are but different manifestations of a single process."

Penfield in 1924 reported an interesting case:[12] a child of 7 months, previously normal,

became ill with otitis media, intermittent fever and vomiting. By the age of 16 months, at which time he was admitted to the hospital, the head was enlarged, the baby was blind and had papilledema and congestion of the retinal vessels. Forty-five cubic centimeters of amber fluid were removed from the subdural space and replaced with air. Roentgenograms showed that the air was not confined in a sac, but that it passed backwards and forwards over the surface of the brain, depending on how the patient was tilted. Passage of air was not altogether free, and it was possible to demonstrate adhesions, both on roentgenographic examination and by the fact that phenolsulfonephthalein introduced into one side did not pass to the other. Following repeated aspirations Penfield's patient improved and at the age of 3 years seemed normal as to mental development, but had some residual impairment of vision. Penfield thought the exudation of fluid to have been caused by the earlier inflammatory process.

Dandy[15] states that subdural hygroma "is about as frequent as subdural hematoma. . . . The two most frequent causes are trauma and extradural, usually mastoid, infections. . . . The fluid, however, remains sterile and acts in every way like that of the traumatic form."

Ford[16] believes subdural hydromas can be regarded in some cases as a reaction due to the extension of an inflammatory process through the dura. He saw one case in which thrombosis of the lateral sinus was associated with two localized subdural collections of fluid.

No discussion of this entity would be complete without reference to Rosenberg's monograph[17] on pachymeningitis hemorrhagica interna. From an analysis of a large number of cases, some occurring in conjunction with meningitis, others not, Rosenberg concluded that neither trauma, hemorrhagic diathesis, nor infection (such as bacterial meningitis) could yield entirely satisfactory explanation for the phenomenon. He finally proposed, as a probable explanation, the occurrence of cavernous sinus thrombosis. However, the autopsy protocols of his cases make no mention of cavernous sinus thrombosis having been noted in his patients.

McKay, Morissette, Ingraham and Matson[4] have recently reported nine patients convalescing from influenzal meningitis in whom collections of subdural fluid were found.

Anatomic and Physiologic Considerations: Astonishingly little information is available concerning the subdural space. Studies by Sayad and Harvey[18, 19] on the one hand and on the other by Leary and Edwards[20] seem to have established the following facts:

While the pia is richly supplied with blood vessels, the arachnoid is made up of cells which are probably ectodermal rather than mesodermal in origin; this is perhaps responsible for the relative impermeability of the arachnoid membrane, and in part for its ability to limit the extension of infection from the subarachnoid to the subdural space, or vice versa.

It seems plausible that active infection within the subarachnoid space may produce inflammation of the overlying pia-arachnoid sufficient to alter its permeability and permit transudation of fluid to the subdural space. If the arachnoid is severely damaged, it seems likely that red cells, white cells and occasionally bacteria can ooze out into the subdural space.

Once in the subdural space what happens to this mixture of cells and protein-containing fluid? Zollinger and Gross[21] carried out some experiments to clarify this point in connection with subdural hematomas. They showed that blood cells mixed with cerebrospinal

fluid and incarcerated in the subdural space lyse in an average of 16 days. Thus, a solution of increasing protein content is produced, with sufficient rise in osmotic pressure to draw fluid from the neighboring subarachnoid space.

Resorption of fluid and protein from the subdural space must of necessity be slow, since the only blood supply to the subdural space is the capillary network of the dura, the arachnoid being devoid of both blood vessels and lymphatics. Furthermore, the subdural effusion must compress these very blood vessels and slow up resorption.

Perhaps the severity and extent of the damage to the arachnoid determine the quantity and the composition of the fluid in the subdural space. Whether "membranes" form may very well, in turn, depend upon the protein of the subdural effusion and the degree to which increased intracranial pressure interferes with the removal of this protein.

Based on these considerations, a rational approach to therapy in these patients would seem to be to perform subdural taps in patients with meningitis whenever a subdural effusion is suspected, and to remove the fluid as it accumulates. When the subdural lesion is thought to have been present for some time, surgical measures should probably be seriously considered, as in the case of a subdural hematoma.[9] Perhaps such fibrin clots might best be treated with one of the new fibrinolytic enzymes,[22] according to the method now employed in empyema and hemothorax.

Analogy with Pleural Effusions: The present investigators have chosen to refer to this clinical entity as subdural effusion, partly in deference to Penfield,[12] who so named it in 1923, and partly because it seems analogous to the much commoner entity of pleural effusion. Surprisingly, there does not seem to be any good discussion in the literature on the pathogenesis of pleural effusions. On many points the resemblance between subdural and pleural effusion is striking: occurrence of the effusion by preference after the acute phase of the underlying inflammatory process is past; occurrence, in both locations, of sterile as well as nonsterile effusions; tendency of the fluid to reaccumulate after its removal by aspiration; development of compact fibrinous exudate in some patients but not in all. There is also great similarity between the pathologic process seen in the subdural space and that puzzling type of empyema known to physicians of the prepenicillin era as "pleuropneumonia,[23] where the fibrinous pleurisy was out of proportion to the underlying pulmonary consolidation, and where the course of the disease was characterized by chronicity and by recurrent bouts of septicemia.

The frequency with which the subdural fluid is bloody in contrast to the pleural fluid may well be due to the peculiar anatomy of the subdural space, where the "bridging veins" of the pia cross the subdural space unprotected and exposed to damage by stretching, as well as by any neighboring inflammatory process.

Conclusion and Summary

Twenty cases of subdural effusion are presented occurring in infants under the age of 14 months during their convalescence from acute bacterial meningitis due to H. influenzae type b, D. pneumoniae, paracolon bacillus and Ps. aeruginosa.

The incidence of these effusions must be quite high, since at least 20 out of 43 cases of meningitis under the age of 2 years had fluid in the subdural space at some time during their hospital stay.

The authors believe that subdural taps should be performed on admission for diagnostic purposes whenever the patient has been treated with antibiotics before coming to the

hospital, and has no organisms in the spinal fluid at the time he is first seen, as well as in all patients who give evidence of prolonged fever, focal neurologic signs, convulsions, etc., following meningitis.

The trauma incident to subdural taps is probably not itself responsible for causing subdural effusions, since in most cases fluid was present at the first tap.

The matter of age incidence needs investigation. There is no reason to believe that such effusions are limited to infants. The possible presence of a subdural effusion should be considered in an older patient whose convalescence from meningitis is slow, accompanied by prolonged fever, headaches and any suggestive focal neurologic signs.

The authors' experience, as well as a review of the older literature, indicates that from the confusing clinical entities known as subdural hygroma, pachymeningitis hemorrhagica interna, etc., one group can be singled out as occurring on the basis of an underlying infection. Its frequent occurrence in recent years is owing to the high survival rate in bacterial meningitis.

The actual pathogenesis of this lesion; the incidence of loculated fluid; the incidence of "membranes"; the possible influence of different treatment regimens on the occurrence of this syndrome; the possibility suggested by analogy with "pleuropneumonia" that subdural effusions, when infected, may serve as foci for later recurrences of meningitis; the possible influence of early recognition and treatment of subdural effusions on the ultimate prognosis in meningitis are matters for the future to determine.

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SPANISH ABSTRACT

Efusiones subdurales complicando meningitis bacterianas

Veinte casos de efusión subdural ocurridos en infantes menores de 14 meses durante la convalecencia de meningitis bacteriana aguda debido a H. influenzæ tipo b, D. pneumoniæ, Bacilo paracolon y Ps. aeruginosa, son presentados en éste reporte.

La frecuencia relativa de éstas efusiones debe ser bastante alta, puesto que al menos 20 de 43 casos de meningitis en pacientes menores de 2 años, demonstraron tener fluído en el espacio subdural en algún instante durante el período de hospitalización.

Creemos que punciones subdurales deben practicarse con propósitos de diagnóstico al ser admitido el paciente, cada vez que éste haya sido tratado con antibióticos antes de venir al hospital, y no demuestre microorganismos en el líquido céfalo-raquídeo cuando se le vé por primera vez, y también en todos aquellos pacientes que han manifestado fiebre prolongada, signos neurológicos focales, convulsiones, etc., consecutivas a una meningitis.

El traumatismo causado por las punciones subdurales no fué probablemente cáusa de efusión subdural, puesto que se encontró fluído en la mayoría de los casos, en la primera punción.

El asunto de la frecuencia relativa respecto a la edad necesita ser investigado. No hay razon que haga creer que tales efusiones se limitan a infantes. La posibilidad de la presencia de efusión subdural debe considerarse en pacientes mayores, cuya convalecencia de meningitis sea lenta, acompañada de fiebre prolongada, cefalalgias y cualquier signo neurológico focal sugestivo.

Nuestra experiencia, así como la literatura anterior, nos llevan a creer que de entre las muy confusas entidades clínicas conocidas como higroma subdural, paquimeningitis hemorrágica interna, etc., hay un grupo que se puede aislar como ocurriendo a base de una infección subyacente. La frecuencia con que se ha observado en años recientes se debe al alto porcentaje de curas en casos de meningitis bacterianas.

La actual patogénesis de la lesión; la frecuencia de fluído en lóculos; la frecuencia de "membranas"; la posible influencia de distintos regímenes de tratamiento en la ocurrencia de este síndrome; la posibilidad sugerida por analogía con "pleuropneumonia" que las efusiones subdurales, cuando se infectan, pueden servir de focos para meningitis recurrentes más tarde; la posible influencia del diagnóstico y tratamiento precoz de las efusiones subdurales en el prognóstico ulterior en las meningitis, son todos problemas que han de ser resueltos en el futuro.

A HOME PLAY AND OCCUPATIONAL PROGRAM FOR THE BEDFAST CHILD; THE COUNTERPANE COURSE

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THE value of recreational therapy for children whose condition requires long continued bed rest or confinement at home is universally accepted. These children are denied the usual outlets for energy and deprived of the normal opportunities for achievement in the eyes of their colleagues. Systematic "play programs" are now recognized as a useful medium to give the child opportunity for achievement within the limitations of his particular handicap.

Hospitals and convalescent homes have met the problem by initiating play or occupational programs. Under the best conditions, they are conducted by trained workers who are able to understand the personalities and problems of children. In less ideal situations the programs have been under the supervision of well-intentioned but untrained volunteers whose only concept of the problem is that the child should be kept amused.

There are two areas of child care where, for good reasons, play or occupational programs have not been instituted under the best conditions. These are the small wards for children where the employment of a trained full-time teacher would be uneconomical; and secondly, the home in which a child suffers or is convalescing from an illness necessitating long bedrest.

In some cities, one or both of these situations are met by the provision of visiting "play teachers" who inaugurate in the homes or hospitals a program adapted to the needs of each child and supply instructions to the nurse or mother for its continuity between visits.

In areas where such services have not yet begun and in countless homes, there still remain many children whose illness and convalescence is unaided by any planned program of occupational recuperation. The word "planned" is really the keynote of any program of occupational or play therapy. Such programs are not effective when looked on as mere diversion, such as can be supplied by the ten-cent-store coloring books which the mother may provide. Instead their object is to provide a continuing field of interest for the child in which progressive achievement supplies a substitute for the activities denied because of illness.

Because the "Home Service" under qualified play teachers was such a success in Baltimore and since this service could not meet all the demands made on it because of geographic distances within the state, an attempt was made to devise a practical kit, including complete instructions, which could be used in any home under the supervision of the mother or other qualified adult.

The problem was presented to the staff of the Calvert School whose long experience in the correspondence programs of education of children for whom group instruction was

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not available well fitted them for the task. From a series of conferences between these educators and play teachers and pediatricians, there evolved a composite course in home instruction which is the object of this report.

The course has been called the "Counterpane Course" after Robert Louis Stevenson's famous poem. It consists of three booklets and a supply of play materials which will be described later.

The first booklet is a parents' manual and contains the general information the parent needs to put the course to use. The second book is the guide to the course; it outlines the session-by-session program in each activity. The third booklet is an accessory one dealing with projects in paper and cardboard.

The guide book outlines the program in eight activity units beginning with the most elementary and proceeding progressively to more advanced work. Each activity unit is

TABLE 1

LIST OF MATERIALS IN COUNTERPANE COURSE

Manila drawing paper	Felt designs
Construction paper	Leather scrap
Cross-section paper	Leather lacing
Carbon tracing paper	Flat white gimp
Stencil sheet	Flat red gimp
Tag (cardboard)	Round pink gimp
Finger-paint paper	Round blue gimp
Finger paint	Raffia
Show-card colors	Knitting yarn
Crayons	Modeling clay
Paint brush	Mexican pottery clay
Punch	Bracelet core
Scissors	Lanyard hook
Knitting needles	Beads
Crochet hook	Linoleum block
Loom	Wood block
Loops	Paste
Felt	

divided into projects. Thus, in the modeling activity, project #1 concerns modeling with prepared clay, #2 with Mexican clay, #3 with clay which may be fired in a home baking oven, #4 with plaques, #5 with casting in molds. In this way a child may begin any activity unit at a stage suitable for his age and ability. But having started a project, he has the opportunity to continue it in advancing stages which promote a sense of accomplishment.

The entire program includes such projects as: Modeling, Felt work, Drawing and Painting, Weaving, Knitting and Crocheting, Sewing, Paper and Cardboard work, Printing, Puppets and Masks, Carving, Leather work, Reed and Raffia work, and Braiding. In addition there is a large section devoted to projects which can be carried out without the use of supplied materials, such as stamp collection and the culture of seedlings in indoor receptacles.

The course is designed to interest any patient from 7 to 12 years of age. The older child may begin any project in a more advanced activity unit or spend comparatively little

time on the more elementary units until he finds his own level and scope of interest. When this level has been determined, the course proceeds in a systematic manner.

The materials supplied with each set are sufficient to start the child in each type of occupational endeavor. As the interests of each patient are found, more materials and information will be needed. The instruction booklets meet this problem by giving a substantial bibliography of helpful books on each subject and by listing the names and addresses of retailers from whom additional supplies can be obtained.

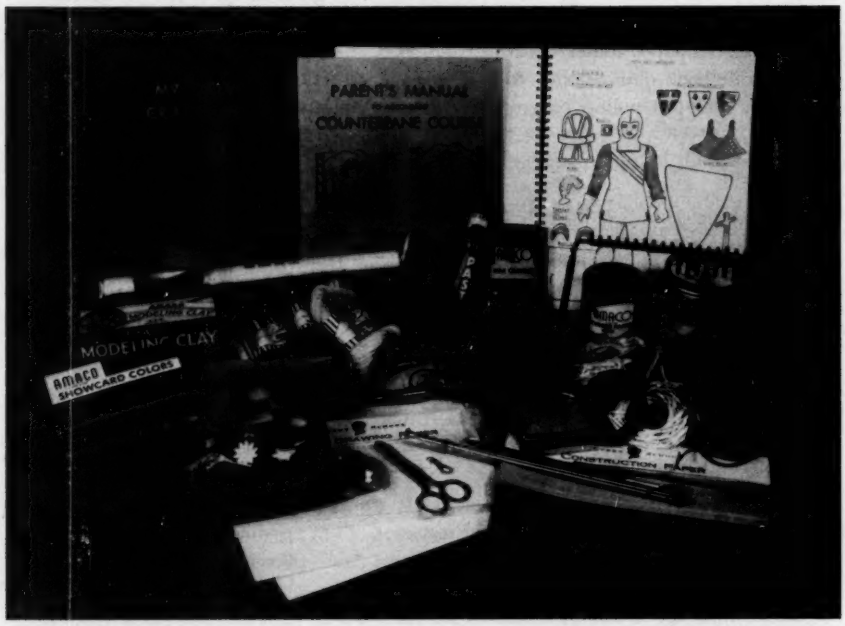

FIG. 1.

These kits include the material enumerated in table 1 and shown in figure 1. They have been made available by the Calvert School, 105 Tuscany Road, Baltimore 10, Md., at a current price of $25.00 including mailing. When it is realized that such a course covers several months of occupational activity, the cost cannot be considered excessive.

These courses were distributed to representative patients in Baltimore convalescing from rheumatic fever. The visiting play teacher left the entire handling of the course to the mother and child, and limited her role to observations concerning the merits or deficiencies of the course. Several practical conclusions have emerged:

1. The course fulfills a definite need for children who cannot benefit from a regular visiting recreational program.

2. The course achieves its greatest benefit where the mother (or her substitute) has good intelligence and at least a high school education.

3. The kit achieves its greatest usefulness when not presented to the child in its entirety. When it is, the patient is overwhelmed by the diversity and amount of material and his interest skips from one to another until all chance for an organized program is

lost. When the contents have been presented in well-graded doses according to instructions, the course covers a year or more of interesting activity.

Pediatricians are frequently asked by the parents of patients suffering from chronic diseases where materials and information for an occupational program can be obtained. The purpose of this course is to provide in the most usable form what the average parents need to institute and maintain a good home program of occupational therapy.

Summary

Many children ill at home or in hospitals are denied the advantage of a planned recreational program. A course has been devised which is complete with adequate instruction books and materials suitable for children 7 to 12 years of age.

Acknowledgment

Credit is due Mrs. George S. Rhoads, Mr. Edward Huey and Miss Mary Madden for assistance in assembling and testing the course.

Spanish Abstract

Programa Para Niños Confinados en Cama. Juego y Ocupaciones Que Pueden Llevarse a Cabo en la Casa. El "Counterpane Course"

Muchos niños enfermos en sus hogares o en hospitales, no pueden gozar de las ventajas de un programa organizado de recreación. Se ha proyectado un curso completo, con libros que proveerán instrucciones, así como material apropiado para niños entre 7 y 12 años de edad.

USE OF THE PERTUSSIS AGGLUTINOGEN SKIN TEST IN A WELL BABY CLINIC

By NOAH BARYSH, M.D.
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THE present investigation was undertaken to evaluate the pertussis agglutinogen skin reaction as a routine procedure to be employed in a well baby clinic. Despite the universality of pertussis vaccination in this country there still is a reasonable percentage (12 to 14%) of infants and children who, after immunization, have limited protection against the disease. A reliable, safe and practical procedure suggested itself in the form of pertussis agglutinogen (agglugen®*) which might unearth these susceptibles for necessary re-immunization.

This pertussis antigen, agglutinogen, has been thoroughly investigated by Felton and Flosdorf[1-6] and their associates reference its antigenicity, specificity in antigen antibody response and clinical application, but there has been a paucity of clinical studies concerning changes in the pertussis agglutinogen skin reaction determined on the same infant prior to and after immunization.

The purpose of this report is to show that: 1. The skin test is a sensitive indicator of the "immune" response produced by prophylactic vaccination. It therefore can serve as a determinant of the efficiency of the "immunizing" material used. 2. The test is a reliable indicator of a specific antibody response as evidenced by testing and retesting the same infant with pertussis agglutinogen prior to and after pertussis immunization.

METHOD OF STUDY

Subjects were 234 normal infants ranging in age from 1 wk. to 9 mo., either on the newborn nursery ward in the Lenox Hill Hospital or in regular attendance at the well baby clinic in the outpatient department of the Lenox Hill Hospital.

Acid-precipitated agglutinogen consisting of 10^9 units of the lyophilized material was added to 1 ml. of NSS, freshly prepared and dissolved. 0.1 ml. of the dissolved material was injected intracutaneously into the forearm of the infant, using a tuberculin type syringe and a ¼" #26 gauge needle. This material, when not in use, was kept refrigerated. The syringes and needles were autoclaved and used solely for this work.

The area of induration was measured at the end of 24 hr. An area of redness and/or induration of 10 mm. or more was considered an immune or positive (PI) reaction. An area of redness alone or induration less than 10 mm. was considered to be a semipositive (WP) immune reaction. No sign of skin response, after 24 hr., over site of injection was a negative (N) reaction.

All injections were performed by the author. At first all readings were made by the author but in the latter part of the investigation, Mrs. Edna Beck, supervisory nurse of the outpatient department, assisted in reading the results.

Group I, a conglomerate group of 100 infants, had either been immunized with 3.5 cc. of N.Y.C. Health Department alum-precipitated pertussis vaccine (20 billion phase I H. pertussis bacilli/cc.) or with 2.5 cc. of an immunizing material consisting of a triple combination of alum-precipitated diphtheria and tetanus toxoids and a suspension of H. pertussis phase I organisms containing 40 billion bacteria/cc., at least 3 mo. prior to skin testing. These injections, a series of 3,

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* Agglugen-Pertussis Agglutinogen supplied through the courtesy of Sharp & Dohme, Inc., J. William Crosson, Medical Director.

were spaced 1 mo. apart. Immunization of this group began at about age 6 mo. Each infant was skin tested with 0.1 cc. of the agglutinogen solution.

Group II, consisted of 134 infants, ranging in age from 1 wk. to 5 mo. This group was subdivided into groups of 20 infants according to age levels. The infants were given intradermal injections of 0.1 cc. of agglutinogen solution prior to pertussis vaccine prophylaxis and retested in a similar fashion with this material at least 3 mo. after completion of pertussis vaccination. The immunizing material used was 2.5 cc. of a triple combination of alum-precipitated diphtheria and tetanus toxoids and a suspension of H. pertussis phase I organisms containing 40 billion bacteria/cc.

Included in the data was information relative to a history of pertussis in the mother.

Discussion

This study of pertussis agglutinogen as a skin test to determine susceptibility (or immunity) to pertussis might also include a brief review of current opinion on this matter.

Several questions in the riddle of immunologic response versus clinical protection in pertussis are, for the present, unanswerable.

For example, pediatricians are uncomfortably aware of the fact that infants given the same dosage of pertussis vaccine may well have variable degrees of protection ranging from a limited response to absolute clinical defense against the disease.

Felton and Flosdorf[5] state that children ill with pertussis may have positive (immune?) skin agglutinogen responses.

Miller[7] states that the agglutination titer following pertussis vaccination rises much more rapidly than it does after recovery from the disease. It has also been established that individuals stricken with pertussis have, at the onset of their illness, absent or low agglutination titers below the level of 1:320 and it has been demonstrated that individuals found clinically immune to pertussis often do not have sufficient circulating antibodies to produce an agglutination titer response of 1:320 or above.[7, 8]

McGuinness[9] made mention that humoral and skin "antibody" response may disappear when the child reaches adolescence even though clinical protection against pertussis persists.

We must, therefore, accept these facts that although certain indications of a skin or humoral response to prophylactic pertussis vaccination, as expressed by the serum agglutination, complement fixation and skin agglutinogen tests, might suggest an antibody-antigen (immune?) response, it does not follow that the changes thus expressed are entirely in accord with clinical experience. Nevertheless, there is a high degree of correlation between these various reactions.[5, 10, 11] The clinical value of some of these tests as determinants of immune response has also been supported by the work of Sako[8] and Miller[12] in pertussis epidemics.

The reliability of the agglutinogen skin test as an index of susceptibility or immunity is intimately associated with pertussis agglutination titer determination.[5, 10, 11] On the other hand, investigation suggests that the skin reaction test may prove to be a more prompt and sensitive indicator of immune response than the agglutination titer reaction, which is slower and less sensitive in certain individuals. Felton and Flosdorf demonstrated in a limited number of cases that children with positive skin reactions to agglutinogen but with absent or low agglutination titers before the test were clinically immune to pertussis. At a later date, varying from 1 to 10 months after skin testing, practically all these children had an agglutination titer above 1:320. Halpern[10] and Bradford[11] have also shown that the percentage of positive skin test reactions in infants vaccinated against

pertussis is higher than the percentage of immediately demonstrable agglutination titer rise.

The effectiveness of pertussis vaccination has been fully reviewed and reaffirmed by the field studies of Miller[7] and Sako.[8] Other workers[12–14] agree that the rise in the pertussis serum agglutinin titer after pertussis vaccination is evidence of immune response. There

TABLE 1

RESPONSE OF 100 INFANTS TO AGGLUTINOGEN SKIN TEST AFTER PERTUSSIS IMMUNIZATION

Immunizing Material Used	No. of Infants Immunized	No. of Immune (PI) Skin Reactions	No. of Negative (N) Skin Reactions	% Positive (PI) Skin Reactions
N.Y. City Health Dept.	41	39	2	95
DPT (Cutter)	59	53	6	90
Total	100	92	8	92%

is also support for belief that testing with skin agglutinogen material, performed either in conjunction with serum agglutinin[5, 10] or complement fixation test, results in an immune response equal to or better than the aforementioned blood determinations. Sauer[15] states, "In the last few years we have discontinued the complement fixation test because its evidence was no more reliable than the simple skin test."

TABLE 2

A. Response of 134 Infants to Agglutinogen Skin Test Prior to Pertussis Immunization.	
1. Infants with positive preimmunization skin tests.	23
2. Ages of infants with positive preimmunization skin tests.	
a. 2 mo.	1
b. 3 mo.	7
c. 4 mo.	7
d. 5 mo.	8
3. Infants with positive skin test with history of pertussis in mother.	10
4. Infants with positive skin test with no history of pertussis in mother.	13
5. Percentage of positive reactions with history of pertussis in mother.	43%
6. Percentage of positive reactions with no history of pertussis in mother.	57%
7. Infants with negative preimmunization skin tests.	111
B. Response of 66 of 111 Infants to Agglutinogen Skin Test After Pertussis Immunization.	
1. Infants with positive skin tests	60
2. Infants with negative skin tests	6
3. Percentage positive reactions	90%

The effectiveness of the material used is indicated by the change in the agglutinogen skin reactions following pertussis prophylaxis in 92% of the cases examined in this series (tables 1 and 2).

The high percentage (17%) of positive skin tests obtained in very young infants prior to pertussis prophylaxis is probably due to the proved placental transmission of serum antibodies against hemophilus pertussis. The number of women of child-bearing

age carrying H. pertussis antibodies in their serum varies in different communities but the countrywide estimate is less than 50%. Probably not more than 25% of infants are born with circulating antibodies.[12] This figure is in agreement with the author's findings.

Early in this study, when the author discovered a reasonably high percentage of positive skin reactors in the preimmunization group, it was hoped that repeated intracutaneous injections of the antigen might induce a sufficient rise in circulating antibodies to support Felton and Flosdorf's recommendation that repeated skin tests might also act as "booster" mechanisms for immune response. However, this hope was abandoned when it was realized that the passive immunity acquired from the mother is dissipated within six months and that transplacentally acquired antibodies cannot be boosted sufficiently to protect the mucosa of the respiratory tract against the invading organism.

It is unfortunate that there are no published reports which would conclusively prove by clinical field trial that infants, following pertussis vaccination and with positive skin agglutinogen tests, are immune to pertussis. However, the studies referred to in this review inferentially tend to support the belief that pertussis agglutinogen has a limited but nonetheless definite value in pediatrics in separating susceptibles from nonsusceptibles following pertussis vaccination.

Summary

Intradermal skin tests with pertussis agglutinogen were performed on 234 infants.

In one group of 100 infants skin tested with this material, at least three months after pertussis prophylaxis, it was found that 92% had positive (immune) skin reactions.

In a second group of 134 infants skin tested prior to pertussis vaccination, 83% (111) had negative skin reactions. In 66 of these 111 infants tested after pertussis prophylaxis, 92% developed a positive skin response.

The pertussis skin agglutinogen test can be used to determine the efficiency of materials used for pertussis prophylaxis.

The pertussis skin agglutinogen test is a reliable indicator of the immune response of an infant to H. pertussis immunization and is recommended as an effective agent for determining the susceptible infant—one lacking the minimal clinical protection against pertussis—after pertussis vaccination.

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SPANISH ABSTRACT

El Uso de la Prueba Intracutánea con "Pertussis Agglutinogen" en las Consultas Externas Infantiles

Pruebas intracutáneas usando "Pertussis Agglutinogen" fueron realizadas en 234 niños.

En un grupo de 100 niños a quienes se hizo esta prueba, por lo menos tres meses después de haber sido inmunizados contra la tos ferina, se observó que un 92% tenía una reacción positiva o de inmunidad.

En un segundo grupo de 134 niños a quienes se hizo la prueba antes de ser vacunados contra la tos ferina, se observó que un 83%, o sea 111 niños, tenía una reaccíon negativa. En 66 de estos 111 niños a quienes se hizo la prueba después de haber sido inmunizados contra la tos ferina, un 92% desarrolló reacciones positivas.

Esta prueba puede emplearse para determinar la eficacia de los productos usados en la profilaxis de la tos ferina.

Dicha prueba es un indicador fiel de la reacción de un niño a la vacunación con "H. pertussis" y se recomienda como un medio efectivo para determinar el grado de protección obtenida despues de la vacunacion.

66 East 78th Street

ACUTE INFANTILE GAUCHER'S DISEASE

Case Report

By CHARLES LAWRENCE RODGERS, M.D., AND SANFORD HUGH JACKSON, PH.D.
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THE relative rarity of the acute form of Gaucher's disease prompted this report of a case seen at the Hospital for Sick Children. In contrast to at least 150 cases of chronic Gaucher's disease which have been described, only 20 adequately proved cases of the acute infantile form have been reported.[1] Of these 20, two only have been reported from North America.[2, 3] Details of the clinical and laboratory findings of this particularly malignant type of Gaucher's disease need not be elaborated here. Various authors[1,2,4–11] have described the clinical syndrome which, in addition to splenomegaly, hepatomegaly and a rapid course, has frequently associated neurologic manifestations. The neurologic complications usually consist of spasticity, opisthotonus, trismus, dysphagia and laryngeal spasm.

CASE REPORT

J. A., a white female infant, was born following an uneventful pregnancy and labour. Birth weight was 2.8 kg., and no physical abnormalities were noted at that time. Both parents were in good health and this was the mother's first pregnancy. The racial background was English and there was no history suggestive of Gaucher's disease in the immediate relatives.

The infant appeared to develop normally until 3½ mo. of age, at which time the parents first noticed that her breathing had become noisy and rattling, as though she had a quantity of mucus in the pharynx. Soon thereafter, when vegetables and other solid foods were added to the diet, the infant experienced difficulty in swallowing and choked frequently. Although prior to this she had taken thick Pablum well, the Pablum now had to be diluted with milk to enable the infant to swallow it. It was for this reason the patient was admitted to the hospital at the age of 5 mo.

Physical examination revealed a well-developed and well-nourished infant, weighing 6.8 kg. She exhibited a constant inspiratory gurgling noise even when asleep. The temperature, pulse, and respirations were normal. Due to the presence of trismus, it was impossible to visualize the pharynx adequately. All that could be seen was a copious quantity of thick tenacious mucus in the throat. The chest, abdomen and glandular system showed no abnormalities. Aside from the presence of trismus and inability of the infant to sit up at 5 mo. of age, the neurologic examination was negative. The nasopharynx and larynx were explored under anesthesia but except for large quantities of mucus, nothing abnormal was found. Chest roentgenograms and barium swallows were normal.

The patient was discharged 1 wk. after admission with no appreciable improvement and no definite diagnosis. The only therapy that had been employed was repeated suction of the pharyngeal mucus.

At home, the symptoms continued. Three weeks after discharge, the patient developed a loose, nonproductive cough, associated with wheezing respirations and a slight fever. Oral penicillin, prescribed by the outside physician, proved of no avail, the symptoms increasing in severity. Therefore, the patient was readmitted at the age of 8 mo.

Examination revealed a pale, moderately well-developed, poorly-nourished (7.0 kg.) infant, who was listless and apathetic. The breathing was noisy and, as before, excess mucus was present in the nasopharynx. Adequate visualization of the nasopharynx was not possible, again due to the per-

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sistence of the trismus. The abdomen was soft and not distended. For the first time the spleen was palpated 5.0 cm. below the left costal margin. It was smooth and firm. The liver was not palpable, nor were the superficial lymph glands enlarged. Neurologic investigation revealed generalized hypotonia with loss of reflexes, trismus, difficulty in sitting up and inability to stand.

Laboratory findings were as follows: RBC 5 million/cmm., Hgb. 14.2 gm./100 cc., WBC 18.4 thousand/cmm., prothrombin time 15 sec., bleeding time 1 min. and clotting time 5½ min. The blood smear showed a normal differential count but the lymphocytes were reported to be somewhat atypical. The Wassermann test, routine agglutination tests and blood cultures were negative. Intracutaneous tuberculin test 1/40 was negative. Unfortunately, tests for blood lipids were not done.

On the second day of this admission, the patient developed nuchal rigidity, opisthotonos, a fever of 40.0°C. and intermittent attacks of cyanosis. A lumbar puncture was negative. Penicillin and sulfa-

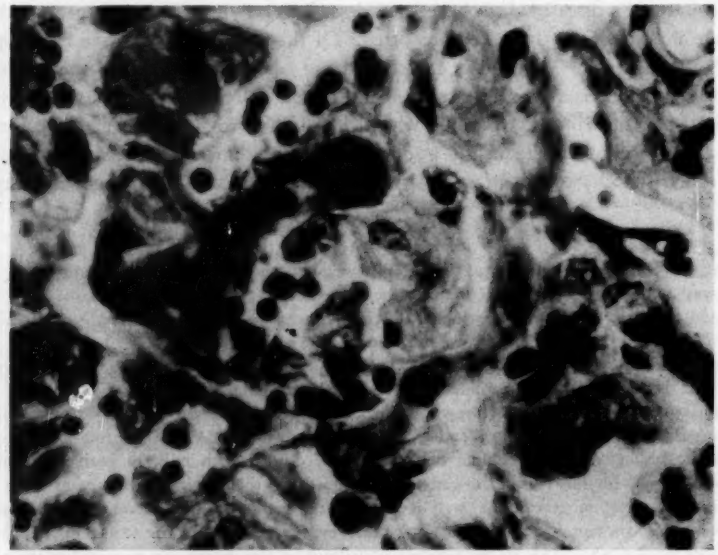

FIG. 1. Thymus gland: Illustrates eccentrically-placed nuclei and fibrillar structure of cytoplasm of Gaucher cells (× 650) (H. & E.).

diazine were administered in large doses with no apparent effect. During the following 9 days, the spleen enlarged to 10.1 cm. below the left costal margin and the liver to 5.0 cm. below the right costal margin. There appeared to be a slight bleeding tendency, as evidenced by 2 small, apparently spontaneous hemorrhages over the right jaw and left mid-leg. These disappeared and there was no recurrence. With the exception that the platelets were decreased in number, repeated blood smears were negative. A sternal marrow puncture revealed both normal total nucleated and differential counts with no unusual cells being seen in any of the smears studied. RGs of the long bones and skull were normal.

During this period, frequent suction was necessary to remove the thick mucus that accumulated in the throat. By 4 mo. after admission, the intermittent cyanotic attacks had increased in severity and number, and were accompanied by choking spells. Fever was persistent and ranged between 37.2° and 38.8°C. Five days later, rales and rhonchi developed in the chest, and the choking and cyanotic attacks became severe. In one of these attacks on the 107th hospital day, the respirations and heart beat ceased suddenly.

Postmortem examination revealed no organic obstruction or abnormality of the nasopharynx, larynx or trachea. The lungs showed small patchy areas of consolidation about

the bronchioles. The liver, spleen and mesenteric and mediastinal lymph nodes were enlarged. The liver weighed 433 gm. (normal 260 gm.), its external and cut surfaces showing no abnormalities other than extreme pallor. The spleen weighed 233 gm. (normal 20 gm.); it was firm, smooth and a light reddish-purple colour with smaller superimposed areas of dark purple discolouration.

Microscopically, the immediate cause of death was attributed to an acute purulent bronchitis. The outstanding feature, histologically, was the presence of large numbers of Gaucher cells in most of the organs studied. These cells were typical in all respects. They were huge, polygonal cells with pale pink cytoplasm and one or more small hyperchromic,

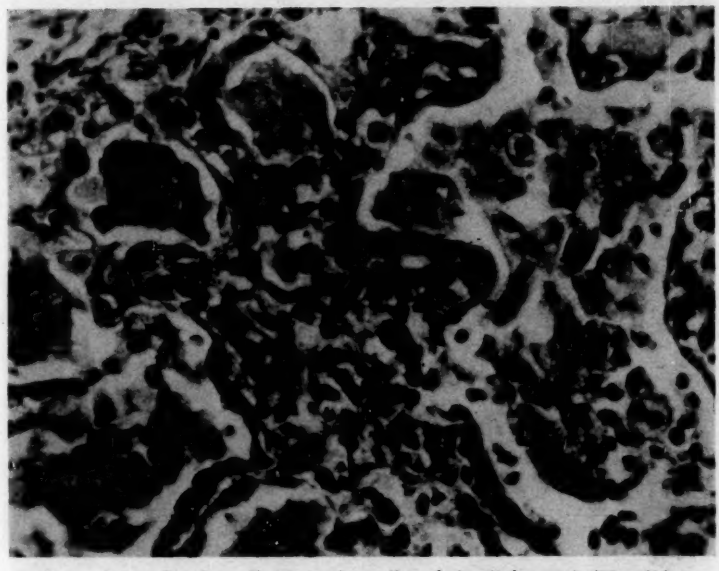

FIG. 2. Lung: Gaucher cells in alveolar walls and alveoli (× 300) (H. & E.).

eccentrically-placed nuclei. The cytoplasm exhibited a wrinkled or fibrillar structure, the stria often running in transverse bands. Various fat stains failed to demonstrate the presence of the neutral fat or lipoids in these cells.

These Gaucher cells were found in great numbers in the lungs, thymus, liver, spleen and lymph nodes and to a lesser degree in the lymphoid tissue of the intestine, adrenals and bone marrow. In the lungs, these cells were found both in the alveolar walls and in the alveoli themselves, to such an extent in the latter that in many areas the lung presented the appearance of consolidation. The large bronchi contained many of the cells mixed with secretions. None was found in the heart, pancreas or kidneys. Wherever the cells had collected they had resulted in compression or displacement atrophy of the parenchyma, the degree of damage varying considerably from tissue to tissue, depending upon the size of the accumulation of the abnormal cells (Figs. 1-5). Careful search of the representative sections of the brain revealed neither Gaucher cells nor evidence of any peculiar or characteristic changes in the pyramidal cells of the cortex.

Halliday et al.[12] demonstrated that the ceresin from the spleen of a case of Gaucher's

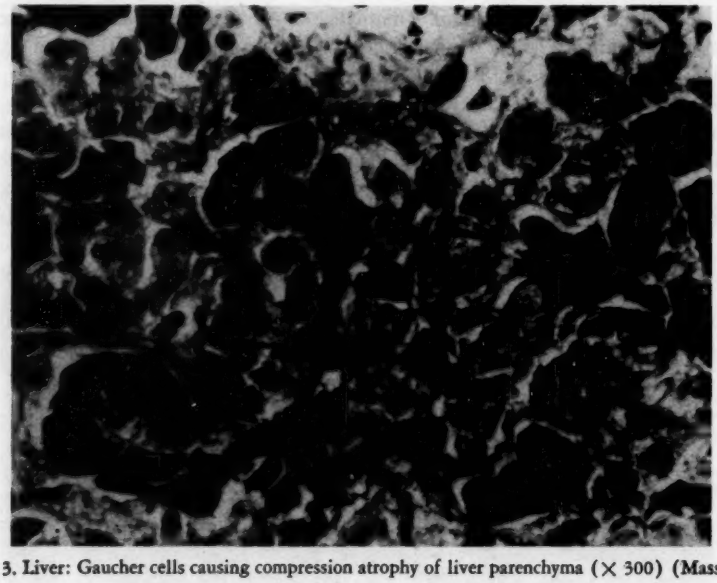

FIG. 3. Liver: Gaucher cells causing compression atrophy of liver parenchyma (× 300) (Masson).

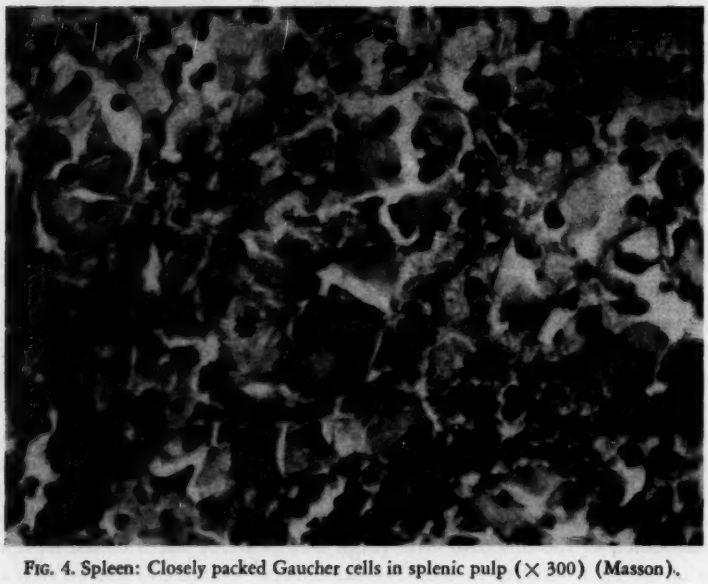

FIG. 4. Spleen: Closely packed Gaucher cells in splenic pulp (× 300) (Masson).

disease contained glucose as the carbohydrate constituent, the normal carbohydrate portion of ceresin being galactose. There has been ample confirmation of the occurrence of the abnormal glucosido-cerebroside in Gaucher's disease.[13–15] In this case, the total lipoid of the liver was approximately normal, being 5.08% of the fresh weight, and the spleen contained 5.62% of lipoid or nearly double the normal amount. The ceresin content of the liver was 0.52% while the spleen contained 0.9%. Normally, the ceresin content of these organs is insignificant. Furthermore, the ceresin in both the liver and spleen was composed of 73% of the glucosido-cerebroside and 27% of the galactosido-cerebroside.

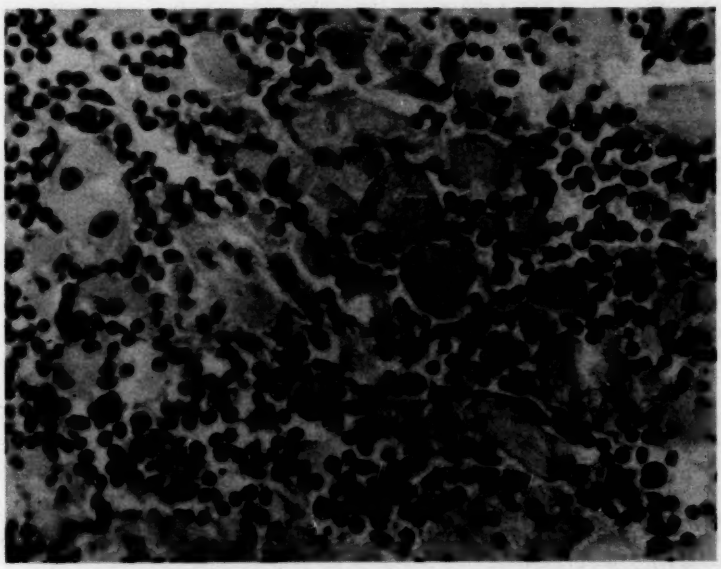

FIG. 5. Lymph node: Gaucher cells in lymphatic tissue (× 300) (H. & E.).

COMMENT

A considerable amount of literature has accumulated in regard to Gaucher's disease in general but so far no evidence has been adduced as to the fundamental etiology or pathogenesis of the condition. The most striking features of the infantile variety of the disease are the malignant course, terminating in death within the first year of life, and the neurologic manifestations.

In retrospect, the signs and symptoms in this case were sufficiently characteristic that if the condition had been more common, a clinical diagnosis might have been made. In fact, a diagnosis of Gaucher's disease had been entertained but was discarded because of the negative bone marrow findings. Bone marrow aspiration is usually a relatively simple means of confirming the clinical diagnosis, as the Gaucher cells seen in a marrow film are typical. However, in this particular case, although a sufficient sample of marrow was obtained, no abnormal cells were seen, even though the films were carefully searched after the diagnosis was established by the autopsy.

It is possible that the excessive amount of mucus in the pharynx of this case was the

result of an attempt on the part of the lung to expel the Gaucher cells and that this mucus, if examined, would have shown the presence of large numbers of these cells. Unfortunately, this was not done.

The familial and hereditary pattern of this disease has been established.[16, 17] There were no other siblings in this case and no family history of a similar affliction could be elicited. Unfortunately, as the parents live some distance from Toronto, they have not been available for investigation as to the possibility of one of them having a latent form of the disease.

Oberling and Woringer[16] have described characteristic changes in the brain of infants dying from the acute form of the disease. These were described as atrophy, vacuolization and mummification of the medium-sized pyramidal cells of the cerebral cortex. Although terminally the case reported here showed the typical neurologic manifestations of this form of the disease, careful search was made in representative areas of the cerebral cortex and none of these changes was found.

Summary

A typical case of acute infantile Gaucher's disease is reported in a female infant, in which the initial symptoms were noted at 3½ months of age and death occurred at 9 months.

Clinical analysis of the liver and spleen showed a considerable excess of ceresin, approximately 73% of which was in the form of glucosido-cerebroside.

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SPANISH ABSTRACT

Forma Aguda Infantil de la Enfermedad de Gaucher; Reporte de un Caso

Se presenta el caso de un niño de 9 meses de edad que falleció a consecuencia de una enfermedad de 5 meses de duración, que se caracterizó por disfagia, exceso de mucus faringeo, rigidez de la nuca, opistotonus, fiebre, esplenomegalia, trismus y debilidad general. El examen post-mortem reveló células típicas de Gaucher en los pulmones, timo, hígado, bazo, ganglios linfáticos, intestinos, médula ósea y las glándulas adrenales. Este caso representa la forma aguda infantil de la enfermedad de Gaucher.

67 College Street

CONGENITAL VERBAL-AUDITORY AGNOSIA

(Word Deafness)

By ISAAC W. KARLIN, M.D.
Brooklyn

THE onset of speech in children usually occurs at about 18 months of age and is earlier in girls than boys. In a previous publication,[1] it was stated that the absence of speech in a child of 2 or 2½ years of age should be considered abnormal, and that mental retardation, hearing disabilities and audimutitas should be considered as possible causes for the delay in the development of speech.

Audimutitas (dumbness without deafness) is used to describe the condition of children who apparently are mentally normal, hear well and understand speech, but do not talk. The condition may be purely functional. The lack of speech may be due either to negativistic tendencies or due to fear reactions, as a result of environmental factors. Organic causes may also play a role. Seemann[2] pointed out that, in children who presented a pathologic fetal position, audimutitas may be of cerebellar and vestibular origin. Synergia being a fundamental cerebellar function, the evolution of speech is also contingent on the cerebellum being intact.

There are cases of delayed speech, however, which cannot be explained on the basis of the three causes just mentioned. Congenital word deafness has to be considered in such cases.

The clinical features of congenital word deafness are as follows:

1. The child does not talk or has only limited speech. This is always the initial and outstanding symptom. It is the child's speech that the parents are primarily concerned about when they bring the child to the physician. The child of 3 or 4 years of age may have no speech at all, or an older child of 6 years of age may have limited and distorted speech. The child's speech may also lack stress and intonation.
2. The child appears to be mentally normal.
3. Physical and neurologic examination is negative.
4. There is a negative history of illness or injury.
5. The child's hearing is the crux of the problem.

At first, the parents are certain that the child is able to hear. As the child grows older, it becomes evident that he is deaf to speech and yet the parents are certain that he is able to hear sound. It soon becomes evident that the limited speech which the child does acquire is through lip reading. In the classical picture the child has normal hearing when tested with the audiometer but is unable to comprehend words by the auditory route.

That this classical picture does not always hold true is illustrated by the following case:

Morris W., aged 6 yr., first visited the Jewish Hospital Speech Clinic with the chief complaints of limited and indistinct speech and hearing defect.

He was a full term child. His mother had no illnesses during pregnancy; she had an uncomplicated 20 hr. labor and a normal delivery. Birth weight was 2.0 kg. The infant's sucking reflex was good but he was difficult to feed; it took an hour to give him the bottle. Feeding difficulties con-

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(Received for publication May 15, 1950.)

tinued for 3 mo.; he then began to pick up and gained weight rapidly. At 6 mo., his weight was 3.6 kg. He had been taking cod liver oil and orange juice since the age of 1 wk.

The father, aged 42 yr., mother, aged 39 yr., and sister, aged 10 mo., were all well.

Morris sat up at 10 mo., had his first tooth at 10 mo., stood at 15 mo., and walked at 22 mo. He did not speak until 4 yr. of age. Toilet training started at 1 yr. but was stopped because he did not seem to understand what was wanted of him. Stool and bladder control came at 3 yr. of age.

His parents were certain that at 11 to 12 mo. of age, Morris awoke on hearing footsteps or any other type of noise. Until 2 or 3 yr. of age, his parents did not notice anything unusual about Morris except the lack of speech and a shyness toward strangers. Between 3 and 4 yr. of age it was noticed that the child was unresponsive except when he could see his mother's face. At about 4 yr. of age he was seen by the family physician whose impression was that Morris did hear.

It was about this time that Morris began to talk using single words. He talked very little and when the parents spoke to him, they were in doubt whether he heard speech or whether he was just unresponsive. At 5 yr. of age parents were certain that the child lip read. They were referred to an otolaryngologist. An audiometer test was done and parents were told that the child was deaf with a 95% hearing loss. The parents were shocked. Shortly thereafter another otolaryngologist was seen and the audiometer test repeated with the same result. Tonsillectomy and adenoidectomy were performed at 6 yr. of age. Radium therapy was given followed by several tubal inflations. There was no improvement in hearing. A hearing aid was secured but the child was unable to use it, complaining of too much noise. It was at this time that Morris was first seen at the Jewish Hospital Speech Clinic.

Additional history obtained from the parents revealed that the child's speech had improved a great deal between 5 and 6 yr. of age, although he had no speech therapy. When Morris listened to the radio, he knew the difference between speech and music, although in the case of speech he did not know its meaning. Since 5 yr. of age Morris has attended a private kindergarten. He gets along well with the children and there are no behavior problems at home or at school. He is a happy child at home, but shy with strangers. His parents are well adjusted and intelligent. They understand Morris' problem and are cooperative and eager to help the child in every possible way.

Examination

Morris, at first shy and somewhat ill at ease, soon became friendly and cooperative. The physical and neurologic examination was negative.

It was immediately evident that Morris lip read well and responded better when questioned by his mother or father. He is right-handed and has never showed any tendency toward left-handedness. His speech was distinct but limited, using 2 or 3 word sentences. There were slight articulatory defects such as a labial "r" and the omission of the "t" and "d" sounds in the medial position. His voice was somewhat husky and he spoke in a monotone.

Voice test elicited no response. The following experiment was tried: A clinician stood behind the child and snapped her fingers at irregular intervals while another clinician tapped his hand at the same time. The child was requested to withdraw his hand when he heard the snap; otherwise, the clinician would tap his hand. The "game" was explained thoroughly to the child by his mother and, after the response was established, he would withdraw his hand when the fingers were snapped behind his back, regardless of whether the clinician in front of him attempted to touch his hand.

Another experiment was tried. Three toys, a snapper, rattle and horn, were placed on a table. The toys were shown to the child and it was explained to him that he should identify the toys by their sounds. He was then placed 15 feet away with his back to the table. When a sound was made with a toy, Morris would turn around, and pick out the appropriate toy.

This was a child who lip read and heard sounds but was unable to comprehend words by the auditory route. A tentative diagnosis of congenital verbal auditory agnosia (word deafness) was made. He was referred for additional tests. The result of these tests were as follows:

I. Psychometric examination:
   1. Revised Stanford-Binet L.—4 yr., 9 mo., I.Q. 75.
   2. Picture Vocabulary—4 yr.
   3. Goodenough drawing of a man—5 yr.
   4. Vineland Social Maturity Scale—4 yr., 6 mo.
   5. Wide-Range Achievement Test
      a. Reading grade: 1.2. Grade: 1A

Age equivalent—6 yr., 2 mo.

b. Spelling Grade: 0:0

c. Arithmetic Grade: 1.2. Grade: 1A

Age equivalent—6 yr., 2 mo.

The conclusion drawn from the psychometric examination was that the test findings would classify the child's retardation as dullness rather than feeblemindedness. Apart from the test findings, however, persons coming in contact with the child judged him to be at least normal if not above normal in intelligence.

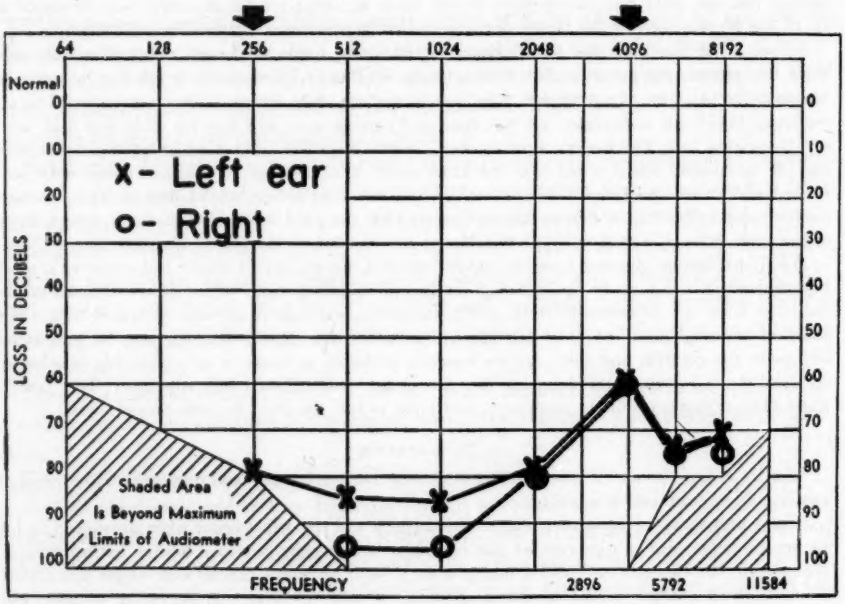


CHART 1.

II. Hearing tests:

Several audiometric tests were done (see chart 1). The final conclusion was that complete functional tests revealed a profound nerve deafness, bilateral 98.4% on each side and a total absence of nystagmus with the cold caloric test. Diagnosis: congenital deafness.

III. Roentgenographic examination:

Roentgenograms of the wrists were negative. Skull RGs revealed normal sutures, vascular and convolutional markings. A large venous lake was seen in the anterior parietal region superiorly. The sella turcica was intact.

IV. Electroencephalography:

Deviations from a strictly normal electric pattern for the age were seen in: (1) greater than usual per cent-time of potentials slower than 8 sec.; (2) greater than usual bilateral asynchrony and base line irregularity. Impression: activity slightly slower than normally expected for the age.

The audiometric findings made untenable the diagnosis of congenital verbal auditory agnosia. The following questions, however, remained unanswered:

1. How was it possible for a child with a hearing loss of 98% to pick out an appropriate toy by hearing the sound without visual aid?

2. According to the audiometer, the child was deaf. How did he acquire speech without help?

3. Presumably the child has congenital deafness. How does one explain the audiometer findings of complete loss in the low and middle frequencies, and a slight rise in the high frequencies?

To obtain a possible answer to these questions and to give the parents the best possible advice as to therapy, the child was referred to Dr. William G. Hardy, Director, Hearing and Speech Center, The Johns Hopkins Hospital. Dr. Hardy's findings and opinions, directly quoted from his reports, are as follows:

"1. ENT findings are negative. Dr. Lieberman, who examined Morris, has no treatment to suggest.

"2. Morris' ability to pick out the appropriate toy by hearing the sound without visual aid was confirmed.

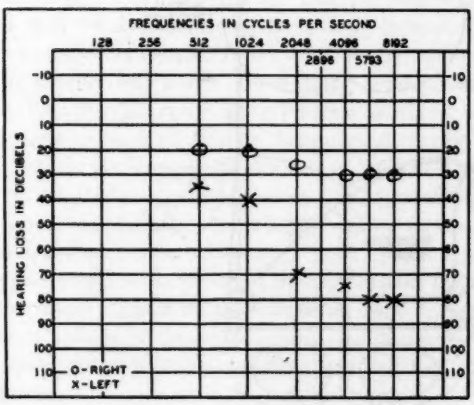
"3. By gross observation, the child's intelligence appears to be of a high order.

HEARING AND SPEECH CENTER
THE JOHNS HOPKINS HOSPITAL
BALTIMORE 5, MARYLAND

HEARING TESTS

NAME W.M. AGE 6 DATE 12-14-49

ADDRESS REFERRED BY



SPEECH-HEARING THRESHOLDS IN DB ABOVE NORMAL:
1. FREE FIELD
2. BINAURAL PHONES
3. RIGHT EAR
4. LEFT EAR

DISCRIMINATION LOSS: %

512 D.V. FORK:
1. REFERRED TO
2. (OPP. EAR MASKED DB)
RIGHT
LEFT

SPECIAL TESTS:

CHART 2.

"4. A copy of the audiometric findings by PGSR is given (chart 2). PGSR is psychogalvanic skin resistance, used as a descriptive of the audiometric pick-up technique. Our findings were obtained by direct reading of PGSR responses; the only difference from our usual technique was the absence of the faradic shock as a conditioning agent. Consequently, I'm not satisfied that our measurements are threshold, but I feel sure that Morris has at least as much hearing as is indicated by the audiogram. Evidently, the principal deviation of the 'hearing' is central and verbal, that is, symbolic; thus, the seeming disparity between findings for sounds and findings for words."

These findings would tend to confirm the original diagnosis of congenital word deafness.

DISCUSSION

It is evident that we are dealing in this case with a defect in auditory and language function that is central in origin. Nielsen[8] has aptly expressed the fact that, in its totality, symbolic thinking and expression is a function of the entire cerebral cortex. It is well established, however, that certain areas in the brain perform certain functions better than the surrounding portions of the cortex. These so-called centers of the brain are not isolated entities, but are closely interrelated. When a certain portion of the brain is not

functioning properly, the rest of the brain will not be able to perform its functions well and symptoms will arise that will mask the basic defect. In the development of speech, granted a normal intellectual endowment, hearing and speech form a closely interrelated function. The normal anatomy and physiology of the auditory pathway, so essential for speech development is grossly as shown in chart 3.

The cochlear division of the auditory nerve arises from the cells of the ganglion of the cochlea of the inner ear and passes into the medulla. Reaching the lower portion of the pons, the fibers divide, one portion going to the dorsal, the other to the lateral cochlear

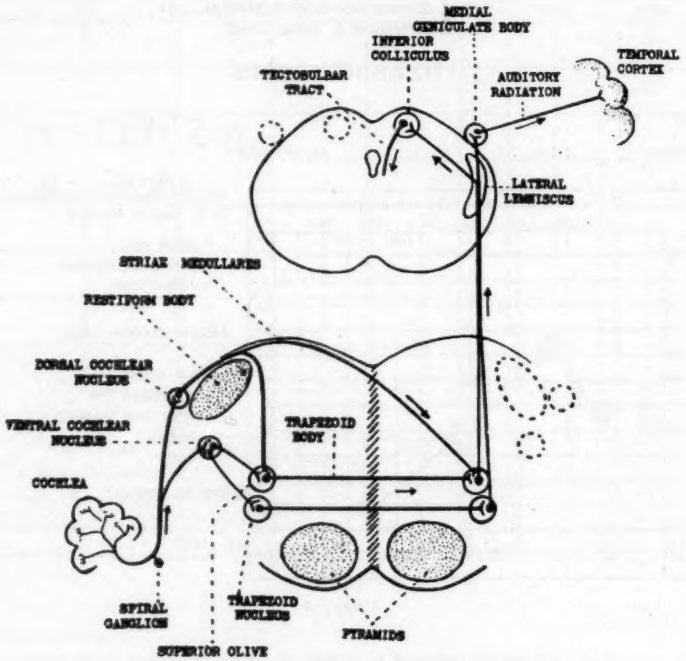


Diagram of the auditory pathway (in part after Gray).
(From Best & Taylor)

CHART 3.

nucleus. The fibers issuing from these nuclei later unite and ascend as the lateral lemniscus to terminate in the median geniculate body. Fibers arising from the median geniculate body form the auditory radiation and ascend in the posterior limb of the intenal capsule to terminate in the temporal lobe of the cortex. The primary center where the auditory impulse arrives is in the transverse gyrus of Heschl, lying in the floor of the lateral (Sylvian) fissure. The impulse then travels further to the adjacent superior temporal convolution or Wernicke's area.

According to Best and Taylor,[4] these two areas constitute the audito-sensory and the audito-psychic centers. In the audito-sensory area, the fundamental auditory sensations,

intensity, quality and pitch, are appreciated. In the audito-psychic area there occurs the analysis and interpretation of auditory sensations and their integration into more complex perception. Goldstein[5] states that the intactness of Heschl's region guarantees the simple acoustic perceptions, while the intactness of the wider field (Wernicke's area) is necessary for perception of the more complex acoustic phenomena of perception of language. Nielsen[3] states that impulses received by the first transverse gyri of Heschl do not enter consciousness. He calls it the site of primary perception. When the impulse reaches Wernicke's area, there occurs recognition of sound in general and of language in particular. This is the site of primary identification. Everyone agrees that for the interpretation of the significance and for the wider interpretation of the meaning of language, the integrity of most of the cerebral cortex is necessary. To complete the picture we may add that these cortical sensory areas are interrelated with the cortical motor areas concerned with speech.

In the adult, a loss or a disturbance in the comprehension or in the expression of language is known as aphasia. Many terms have been used to designate word deafness in the child. Ewing[6] uses the term aphasia, but some of his children had high frequency deafness which might explain the language difficulties that these children presented. Others used the term congenital or infantile aphasia. There is an objection to the use of the term congenital aphasia. In the child, we are dealing not with the loss of a previously existing function but with a failure in the development of a function. To meet this objection, Nance[7] suggests the use of the term idiopathic language retardation. Another term which has been used to describe these cases is psychic deafness in children. Froeschels[8] points out that the term psychic deafness in children is misleading since it may be confused with hysteric deafness or with deafness due to emotional or psychologic factors. Inasmuch as congenital word deafness is not a psychogenic disturbance, Froeschels[8] proposes the term central deafness.

Another objection to the use of the term aphasia in the case of children with congenital word deafness is based on the studies of word deafness in the adult. Head,[9] from his studies of aphasia in the adult, regards a disturbance in the auditory field as belonging to a lower order of functional disintegration than aphasia, and calls it auditory imperception.

Worster-Drought and Allen,[10] taking into consideration the studies of Head, use the term congenital auditory imperception to describe word deafness in the child.

Nielsen,[11] from his studies of pathologic specimens in the adult, also regards word deafness as being on a lower level than aphasia and groups it under agnosia. Agnosia is a disturbance of recognition or identification, while aphasia is the loss of the recognition of the significance of the word. For children with word deafness, Nielsen uses the term congenital psychic deafness but he believes a better term would be congenital verbal imperception.

It is evident that while the language or verbal defect is the initial and most evident disorder these children present, it is the cortical auditory defect for language that is the most striking and outstanding disorder. Taking into consideration the views of Head and Nielsen, that word deafness in the adult is on a lower functional level than aphasia, and working by analogy, it would appear that, at the present at least, a good term for word deafness in the child would be congenital auditory-verbal agnosia. Here, too, it must be pointed out that Nielsen objects to the use of the term agnosia in these cases because agnosia is a loss of a previously possessed function and agnosia of language

belongs to aphasia. The term congenital verbal-auditory agnosia, however, is descriptive in the sense that it indicates that the defect is on a lower order than aphasia and, at the same time, it localizes the defect to the cortical hearing and speech areas.

As to the pathogenesis, since there are no autopsies of these cases, one can only speculate upon the underlying pathology. Worster-Drought and Allen[10] believe that the probable cause for this condition is an aplasia of the post-temporal cerebral cortex. They state that since each auditory nerve is connected with both temporal lobes, the defect has to be bilateral. It would appear, however, that the localization of this defect need not be bilateral. Nielsen,[11] from his studies with adults, states that many cases are on record showing that patients with word deafness have a lesion in the middle third of the first temporal convolution on the major side. Best and Taylor[4] state that the audito-psychic area is mainly unilateral, being on the left side in right-handed individuals and vice versa. Orton[12] states that all neurologists are agreed that a lesion in one brain hemisphere, providing it be the dominant one, is sufficient to cause the disorders of spoken and written language.

The case reported here is believed to be the first in which an electroencephalographic record was obtained. As mentioned, it showed an activity slightly slower than normally expected for a child of that age. One may possibly infer from this that there is either a lack or perhaps a delay in the development of the cortex. Further electroencephalographic studies will be made.

One may compare word deafness in children with "word blindness" (reading disability). Both are defects in the zone of language, but while word blindness is more easily recognized and has been more frequently reported, word deafness is more difficult to recognize, and has been reported less frequently. Undoubtedly, many children with word deafness are diagnosed and treated as deaf mutes or are regarded as mentally retarded children.

It is true, however, that word deafness is actually less common than word blindness. Worster-Drought and Allen point out that spoken language is phylogenetically a much older form of communication than written language and is much less likely to be affected by biologic defects.

Congenital word deafness, like congenital word blindness, is much more common in males than females. The proportion is approximately 5 to 1. It is interesting to note that the same proportion is found among stutterers. The theory that stuttering may be due to a delay in or lack of myelinization of cortical speech areas[13] may also be applied to congenital word deafness.

Treatment

The adult with aphasia usually presents varying degrees of all forms of speech defects. The aphasic patient will manifest defects in comprehension as well as in expression although one form may predominate. The child with verbal auditory agnosia has as his outstanding symptom a defect in verbal expression; however, he may have, in varying degrees, defects in other aspects of language function.

The physician is usually the first one to whom the parents bring the child who does not speak. Once the diagnosis is established, the parents should be made to understand the type of defect the child has and they must appreciate the fact that the child has to be under observation for a period of years. The parents, and later the teachers and speech therapist, must bear in mind that they are dealing with a growing child and that the normal process of growth and development may produce results which no one can

foretell. In the case presented here, Morris developed speech between 5 and 6 years of age without any actual therapy. At home, the child has to be accepted by his parents as essentially a normal child. However, because of his handicap, he has to be given special consideration. To stimulate his attention and perception, toys and games should be used which are of interest to him. The mother should not be tempted to try continually to test his hearing ability. Since the normal tendency to question and chatter (so essential for the development of language) is lacking in a child with word deafness, the parents, especially the mother, should try as much as possible to stimulate his interest in speech by talking to him, reading to him, showing him pictures and describing them to him, the object being to motivate his verbal communication interests.

The usual addage "The child should be seen, not heard" should be changed to "The child should be heard and seen."

The educational approach includes school placement and speech therapy. At one time it was advocated that these children be placed in a school for the deaf. While some of the methods of speech therapy used with the deaf may have to be adopted in treating these children, it would be psychologically wrong to place a child with word deafness in a school for the deaf. The ideal place would be a private school for normal children with small classes and a teacher willing to cooperate and help the child.

Speech therapy is given by a trained speech technician. The main purpose of therapy is to motivate the child's use of language in his daily activities. This is not limited to his speaking habits alone (or lack of them), but the utilization of hearing as well. Children with auditory agnosia may have ignored language because it was meaningless to them. In order to develop auditory word associations, the child should be encouraged to listen to spoken language, and not to rely upon visual and other sensory stimulations.

In cases where the audiometer test is normal, the use of a hearing aid is certainly not indicated. In the case of Morris, a hearing aid was obtained before he came to this clinic. The author has temporarily decided against its use, and Dr. Hardy has concurred in this decision. Artificial methods of increasing the volume of language sounds to a point beyond comfortable listening are worthless, and may be detrimental in the case where there is no hearing loss. When the level of sound is raised to the point of discomfort, the natural reaction on the part of the child will be to develop resentment toward the auditory stimulus. However, the speech therapist may try the use of a hearing tube. One must bear in mind that this tube is not used as an amplifier but rather to bring the auditory stimulus closer to the ear. By using this auditory stimulus in combination with visual symbols, auditory attention and perception are developed and trained.

Depending upon the progress of the child, later on a program of vocational training will have to be considered.

There are no recorded cases in the literature of children with verbal auditory agnosia who have been followed up into adult life. One finds statements to the effect that after a few months of treatment, "the child has made considerable improvement." As mentioned before, some of the improvement may have been due to the normal process of growth and development of the child. It is necessary to have a more thorough follow-up program in order to establish the final outcome of these cases.

SUMMARY

The term congenital verbal auditory agnosia is proposed as a name for congenital word deafness in children.

The clinical features that these children present are: (a) lack of speech or limited

speech; (b) an ability to hear sounds combined with inability to comprehend words by the auditory route.

The defect is apparently in the audito-psychic area or Wernicke's area.

The unusual case of a child with congenital verbal auditory agnosia is described.

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SPANISH ABSTRACT

Agnosia Auditiva-Verbal Congénita (Sordera Verbal)

Los autores sugieren el nombre de agnosia auditiva-verbal para la sordera verbal congénita en los niños.

Los síntomas clínicos que presentan estos niños son los siguientes: a) ausencia del habla o habla limitada; b) facultad de percibir los sonidos, pero ausencia de facultad para comprender las palabras por la vía auditiva.

El defecto radica aparentemente en el área psíquica-auditiva o de Wernicke.

Se describe un caso raro de un niño padeciendo agnosia verbal-auditiva.

1509 Union Street

COMPRESSION OF THE TRACHEA OR ESOPHAGUS BY VASCULAR ANOMALIES

Surgical Therapy in 40 Cases

By ROBERT E. GROSS, M.D., AND EDWARD B. D. NEUHAUSER, M.D.
Boston

MANY vascular malformations in the superior mediastinum have little or no clinical significance, but others assume importance because an abnormal or displaced vessel can compress the trachea or esophagus (or both) and give partial obstruction of these vital pathways. Since methods are now available for thoracic exploration of even the smallest subjects, a new field of surgical endeavor is opened whereby it is possible to correct or readjust such malformations and bring relief of the esophageal or tracheal disturbance. While these abnormalities were once of interest only to anatomists and pathologists, it is now desirable to recognize them during life so that corrective measures can be instituted whenever desirable.

Arterial derangements within the thorax are common, are complex, and can assume many diverse forms; these facts have been impressed upon the authors by an extensive review of the available literature and by the excellent studies which have been made by Dr. Sidney Farber over a period of many years. It would require a presentation of monographic size to list and describe all the anomalies which have been encountered. The purpose herewith is to present only those which have been encountered at the operating table when attempting to relieve an existing tracheal or esophageal compression. The authors are indebted to the many physicians and pediatricians who have assisted in the joint study of these patients. Drs. Carlyle G. Flake and Charles F. Ferguson have been helpful in endoscopic observations when these were required; their gentle and delicate technics have permitted the direct viewing of the interior of the trachea and esophagus with the utmost safety in the tiniest babies.

For the sake of brevity, and without thought of slighting the contributions of others, the literature which is available on the subject will not be itemized or referred to. This report lists the significant points of diagnosis and surgical therapy and the results of treatment in 40 babies and children who have been operated upon at the Boston Children's Hospital for the vascular anomalies under discussion. The material can be divided into five distinct categories, which will be considered in separate sections. As far as is known, the first successful surgical therapy for each of the five malformations was instituted in this clinic.

DOUBLE AORTIC ARCH

While the normal human has an aortic arch which passes anterior and to the left of the trachea and then proceeds as the descending aorta, a small number of subjects are born with a double aortic arch. The ascending aorta bifurcates into two branches, one of which passes in front of and to the left of the trachea, while the other progresses to the right

From the Surgical and Radiological Services of the Children's Medical Center and the Departments of Surgery and Radiology of the Harvard Medical School, Boston.

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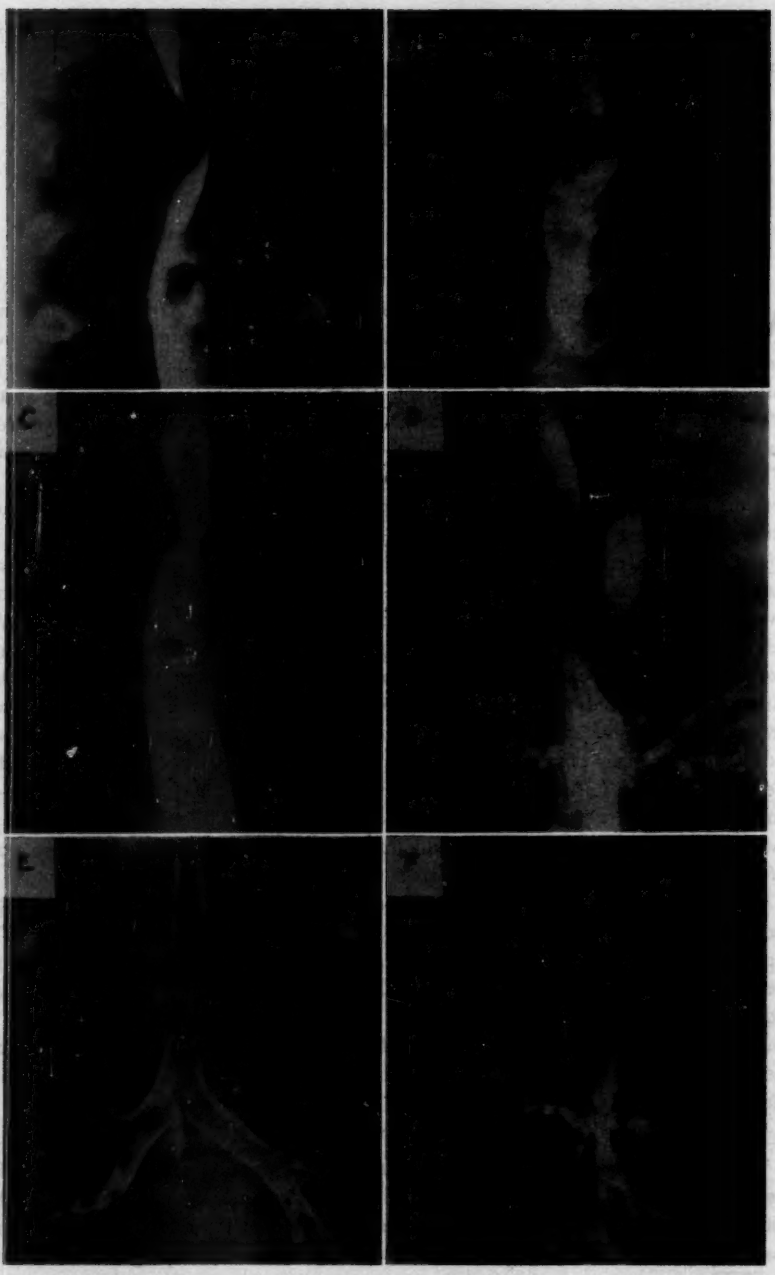

FIG. 1. Typical RGs from cases of double aortic arch (compare Figs. 2, 3 and 4). A. Lateral view, with large posterior compression of esophagus. B. Lateral view from baby with smaller posterior indentation of esophagus. C. A-P view with moderate indentation of both sides of esophagus. D. Combined tracheogram and esophagogram. Trachea is quite narrowed while posterior wall of esophagus is compressed at slightly lower level. E. Visualization of trachea by lipiodol. There is compression of both sides of trachea. F. Lateral view of trachea, showing marked narrowing.

and to the posterior aspect of the esophagus, both limbs then joining to form a descending aorta. In the great majority of cases, the left (anterior) arch is the smaller of the two, and obviously is the one which must be divided at any surgical undertaking (Fig. 2). In a minority of cases, the right (posterior) arch is the smaller of the two and hence is the one which should be severed (Fig. 3). In rare instances a double aortic arch may appear

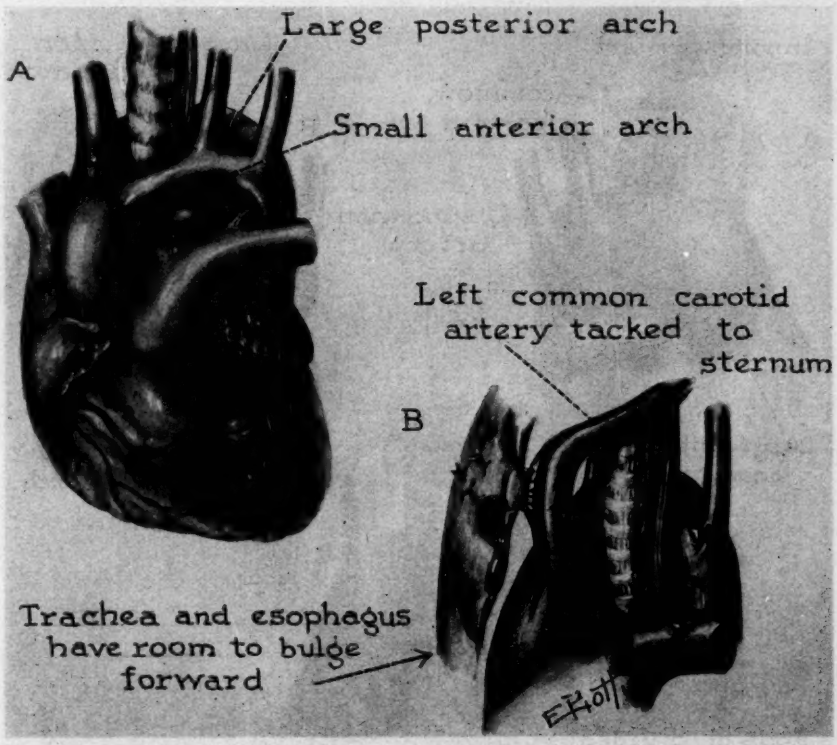

FIG. 2. Double aortic arch with large posterior limb and smaller anterior limb. Of 16 cases with double aortic arch, 9 had this configuration. A. Anatomic arrangements producing constriction of esophagus and trachea. B. Surgical alleviation of condition. Ligamentum arteriosum has been divided to allow pulmonary artery to fall forward. Small anterior aortic arch has been divided to break constricting ring. Left common carotid artery has been tacked forward to back of sternum, so that it will not press upon anterior surface of trachea.

in combination with a descending aorta which lies to the right of the vertebral column (Fig. 4).

It is possible to have a double aortic arch with little or no attendant difficulty, provided the space between the two limbs is relatively large and the encircled trachea and esophagus are thereby given sufficient room. However, most subjects with this anomaly have very little space between the two arches, so that the esophagus and particularly the trachea are greatly compressed. While a bifid arch is compatible with a long life and relatively minor symptoms, the anomaly is usually a serious one, often leading to fatality within the first

year or two of life, because of extreme tracheal obstruction and because of superimposed pulmonary infection which these youngsters are so prone to develop.

Most humans with a double aortic arch have enough difficulties to come to the attention of a physician during infancy. There may be mild to moderate hesitation in swallowing. Of greater importance are the alarming symptoms which come from tracheal narrowing. The respiratory rate may be increased. The baby or child obviously works hard to obtain

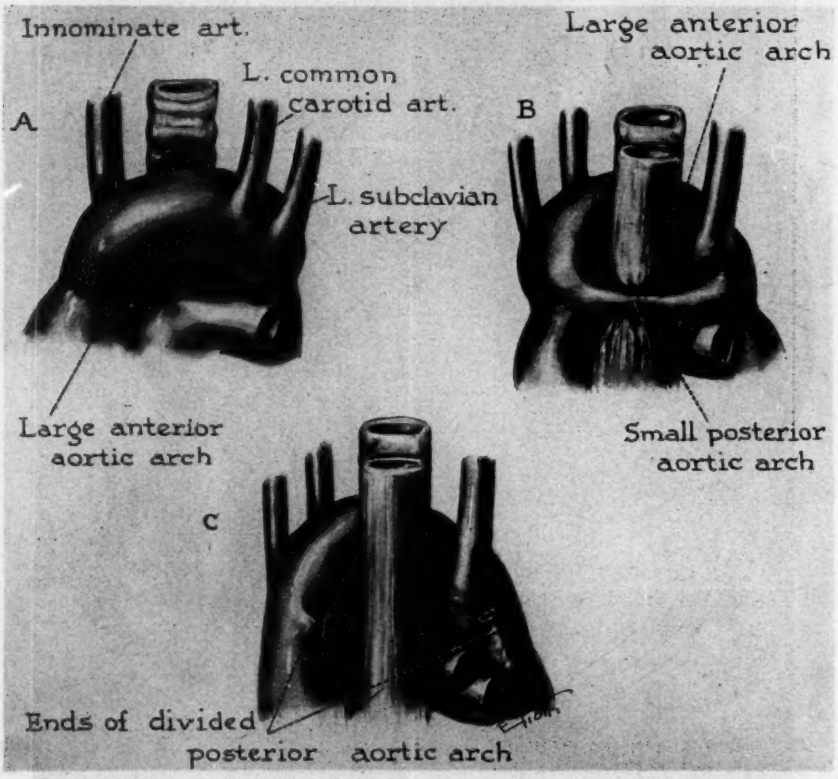

FIG. 3. Double aortic arch with large anterior limb and smaller posterior limb. Of 16 cases with double aortic arch, 4 had this configuration. A and B. Anterior and posterior views of anatomic arrangements, showing encirclement and constriction of trachea and esophagus. C. Surgical cure of condition by complete division of smaller posterior arch.

an adequate exchange of air, an effort which requires use of the accessory muscles of respiration. During inspiration there may be intercostal and suprasternal retraction. A loud wheeze can be heard by stethoscopic ausculation, but usually the noise is great enough to be heard with the unaided ear many feet or yards away. There is apt to be a "crowing" type of respiration, with a marked inspiratory and expiratory stridor. At times there is a rattling or gurgling noise from the lower airway, but even when all fluid can be cleared from the passages, there is a residual noise which is highly suggestive of an obstruction somewhere below the epiglottis. Respiratory distress is often made worse during or im-

mediately after the swallowing of milk or food. These babies have a high tendency to lie with the head in hyperextension, because this position attenuates the trachea and pushes away from its anterior surface any structure which is impinging upon it. If the examiner forceably flexes the head, the exchange of air is reduced or may even be completely cut off, though the movements of the thorax continue. Superimposed upon the tracheal obstruction may be infection or pneumonia which complicates the picture and makes the condition of

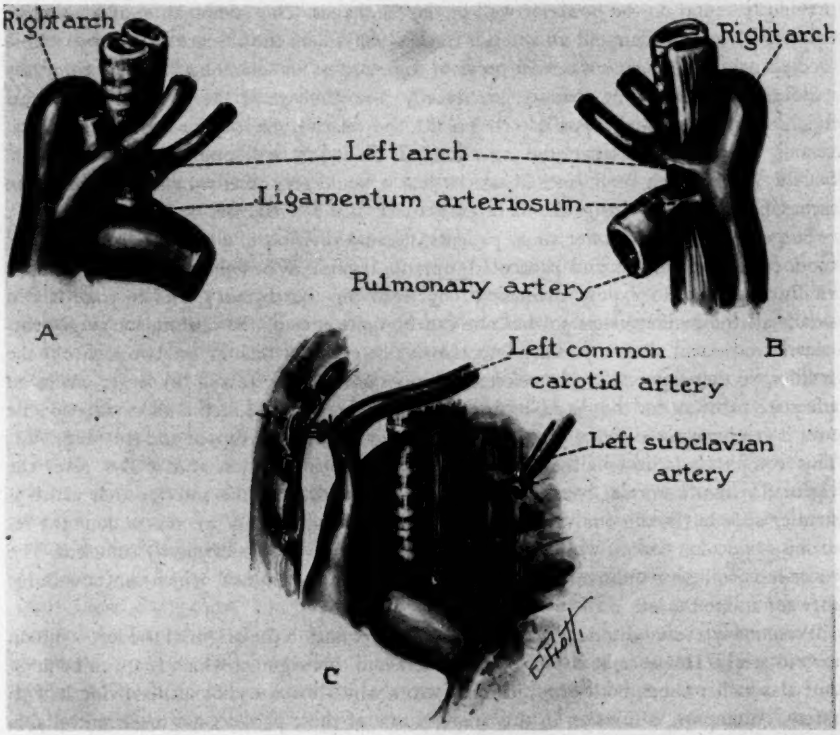

FIG. 4. Double aortic arch, combined with right descending aorta. Of 16 cases with double aortic arch, 3 had this combination. In 1 case there was no lumen in that portion of left arch which lay behind esophagus; in other 2 instances, this segment was patent. A and B. Anterior and posterior views showing anatomic arrangements which give constriction of trachea and esophagus. C. Surgical relief of condition by division of ligamentum arteriosum, division of left arch (posteriorly), division of left subclavian artery and tacking left common carotid forward so that it is pulled away from trachea. All these steps give more room for esophagus and trachea.

the child more grave. Respiratory symptoms may be serious enough to demand oxygen therapy.

By roentgenologic examination, important data can be gathered in several ways (Fig. 1). Simple films of the chest might show pneumonitis, but they can also give additional evidence suggesting tracheal blockage. During inspiration there may be poor or irregular aeration of the lungs, whereas during exhalation the lungs may be hyperaerated. Lateral films of the thorax, if made at precisely the correct exposure, can outline the trachea be-

cause of the air which it contains. The upper trachea is of normal calibre, but the lower portion has a marked reduction of its lumen and is displaced forward. A swallow of barium shows indentation of the posterior wall of the esophagus at the level of the third or fourth thoracic vertebra, this defect being horizontal or nearly so. Injection of lipiodol® into the trachea gives clear delineation of this structure. Antero-posterior films show a definite compression of both sides of the trachea in its lower third, but lateral views show the constriction more strikingly. This narrowing is at a level close to that where the defect was previously found on the posterior wall of the esophagus. This combination of a posterior esophageal compression and an anterior tracheal defect (in the absence of a demonstrable mediastinal mass) is almost certain proof of some sort of an encircling "vascular ring." By various roentgenographic changes, particularly from the size of the posterior esophageal indentation, it is usually possible to predict the relative size of the two arches. Intravenous injection, or retroarterial injection, of diodrast® will outline the arch system, but this has not been done, since it was felt that it would give excellent visualization of the arches, but would not change the therapeutic attack in any given case.

Surgery has much to offer these patients, because division of one arch provides more room for the esophagus and particularly for the trachea. When the chest is opened, it is vitally important to expose adequately (by removing the thymus), and to trace out in detail, all the major vessels so that one can be quite sure of the anatomic arrangements which are present. It is especially important to determine which of the two arches is the smaller, so that this one can be selected for division, thereby leaving the larger one as an adequate pathway for the distribution of blood. If the posterior arch is the smaller of the two, it can be exposed in the posterior mediastinum, and can be ligated and cut (Fig. 3C). This completely relieves all esophageal and tracheal constriction and it also gives the vascular system a normal configuration. More commonly, it is the anterior arch which is smaller and thus is the one which must be severed (Fig. 2B). When this is done the remaining vascular system, while not anatomically normal, is physiologically sufficient. The procedure will give sufficient room for the esophagus and trachea, which can now bulge forward and to the left.

Presumably a left (anterior) arch could be cut proximal to the origin of the left common carotid artery. However, it is probably wise to avoid this segment which is apt to be large and also rather short, both of which are factors which make it difficult to divide it with safety. Attempting a division in this area for one of these patients led to uncontrollable hemorrhage and fatality; the authors are reluctant to ever try it again. Furthermore, if this arch is divided to the right of (proximal to) the origin of the left common carotid artery, any subsequent flow of blood into the carotid must depend entirely upon the intercommunication of the two limbs as they join to form the descending aorta. In some cases this orifice is quite small and might lead to an insufficient distribution into the left common carotid artery. Hence, a proper supply to the left common carotid artery is best provided by dividing the left (anterior) arch between the origins of the left common carotid and the left subclavian artery as shown in figure 2B. This has become the authors' standard procedure. After the arch has been cut in this way, one finds that the remnant of the left arch will course upward and will continue into the left common carotid artery and that these will press against the anterior surface of the trachea like a taut elastic band. It is important to recognize this and to provide forward displacement of this vascular channel by taking several mattress stitches of silk (00 or 000 Deknatel), grasping only the adventitia,

and carrying them forward as stitches which pierce the substance of the sternum. When these sutures are tied up with sufficient tension, the vessel is drawn forward so that it no longer touches the trachea at any point.

In some cases the pulmonary artery has been held in a retrodisplaced position by virtue of its attachment, through the ligamentum arteriosum, to the aorta. This ligament should be divided, to allow the pulmonary artery to fall forward. While this additional step seemed to have little value for some patients, it has certainly been worth while for others.

In those rare cases with a double aortic arch and a right descending aorta, the smaller arch has coursed to the left and posterior aspects of the trachea and esophagus (Fig. 4). Under these conditions, the authors not only severed this left arch in its retroesophageal portion, but also divided the first part of the subclavian artery and furthermore cut the ligamentum arteriosum which was a taut element in the constricting ring.

Of the 16 patients with double aortic arches who have come to operation, 13 had the aorta descending on the left and 3 on the right. Of the 13 with a left descending aorta, there were 9 in whom the left (anterior) arch was the smaller of the two and was accordingly divided, and there were 4 in whom the smaller right (posterior) limb was sectioned. In the 3 patients who had double arches and a right descending aorta, it was always the left (posterior) one which was divided. These 16 patients ranged in age from 1 month to 2 years. The first one was operated upon June 9, 1945. There have been 4 deaths; 2 from hemorrhage at the operating table, 1 from cerebral edema the day following surgery (the child had been dangerously ill and was in an oxygen tent for four months before coming to this hospital), and one from pneumonia 10 days after operation. The 12 surviving patients have been followed for varying lengths of time (up to five years) since operation; they have had extraordinary relief of symptoms. Usually, a marked improvement in the airway has been noted immediately after operation. In all cases, the exchange has obviously been more free and the subject has not had to use the accessory muscles of respiration for ordinary activity. Intercostal and suprasternal retractions have disappeared and the stridor has usually vanished. In a few subjects the respiratory sounds are quiet during resting periods, but are a little more prominent than normal during times of severe straining, crying or other marked exercise. While complete follow-up tracheogram studies over long periods of time have not been made, the impression is that the tracheal airway is markedly improved soon after operation, but that some deformity persists in the cartilages. However, it is reasonable to assume that the removal of all external pressure will now allow the trachea to grow in a more normal way during future years. Long-term studies over a decade or more will probably be required to give conclusive data regarding the ability of the trachea to reform in a satisfactory manner.

To date, the over-all results in surviving patients have been exceedingly dramatic and have proved beyond doubt that the operative attack on this vascular abnormality has great merit. This does not imply that all humans with a double aortic arch require operation, because there are doubtless a few subjects who tolerate the situation in a reasonably satisfactory way through a long life. However, it is probably true that most infants and young children with this abnormality will develop serious or fatal complications so that it becomes highly desirable to undertake surgical correction, if adequate surgical facilities and skill are available.

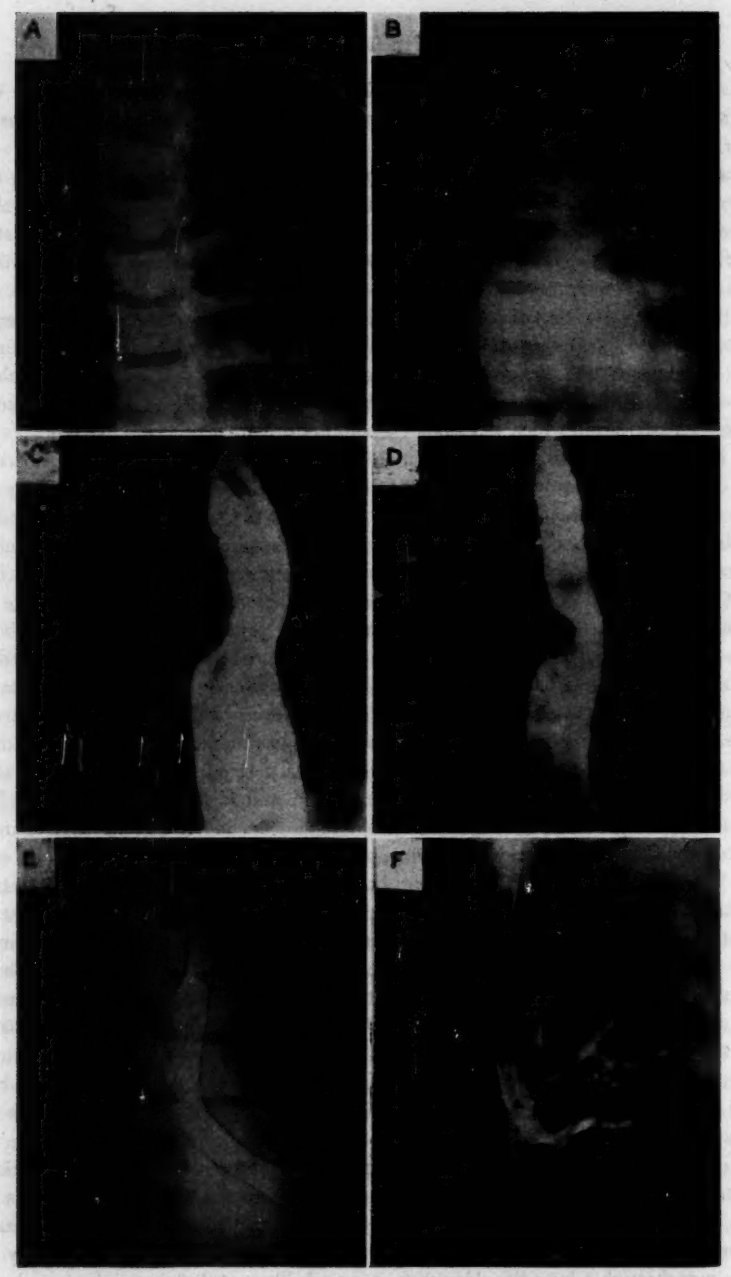

FIG. 5. Typical RGs from cases of right aortic arch with left (posterior) ligamentum arteriosum (compare Fig. 6). A. Plain film showing arch to patient's right (arrows). B. Angiogram visualizing arch passing to patient's right instead of to left. C. A-P view of esophagus with slight indentation on patient's left and larger compression on right, latter being caused by aortic arch (arrows). D. Lateral view of esophagus with deep and narrow posterior indentation which is made by ligamentum arteriosum. E. A-P film of trachea, with compression of its right side by aortic arch (arrows). F. Lateral view of trachea, showing marked narrowing.

Right Aortic Arch with Left Ligamentum Arteriosum

In the development of the human embryo it is the left fourth branchial arch which persists and gives rise to the definitive aortic arch in postfetal life. If, however, the left fourth arch disappears and the right one assumes the role of the main arterial channel leading from the heart, the subject is born with an arch which ascends, passes to the right of the trachea and esophagus, and then continues as a descending aorta which may lie

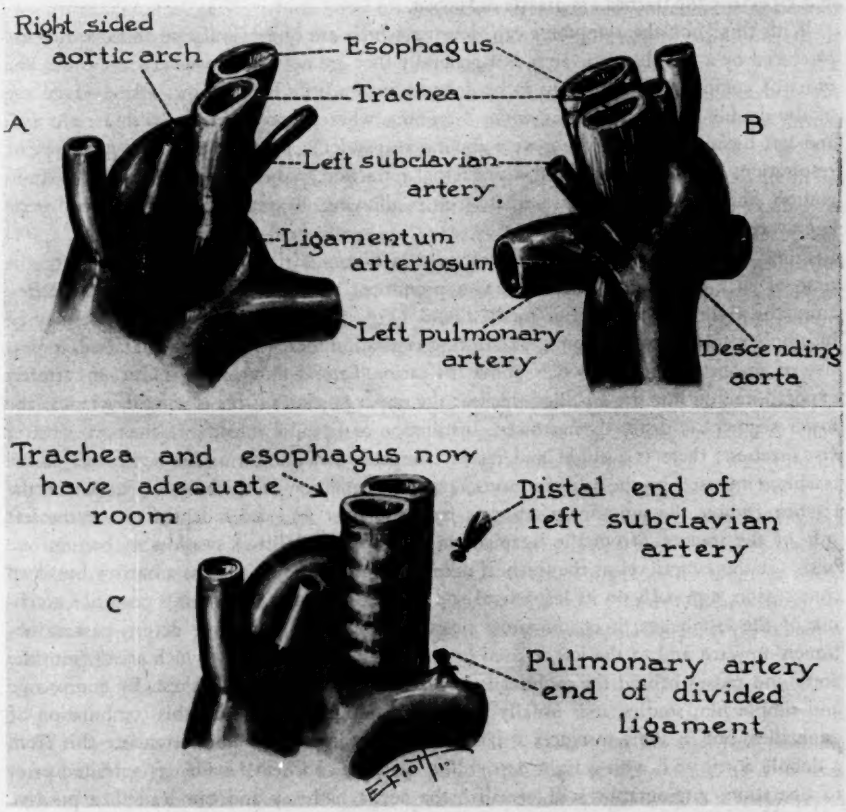

Fig. 6. Right aortic arch with left-posterior ligamentum arteriosum. Seven cases of this sort have been treated. A and B. Anatomic arrangements with constriction of esophagus and trachea. Left subclavian artery and ligamentum arteriosum sometimes arise close to one another from aortic wall and 2 taut structures have tendency to pull out aortic wall into sort of diverticulum. C. Surgical alleviation of anomaly. Ligamentum arteriosum and first part of left subclavian artery have been divided, thus allowing esophagus and trachea to displace posteriorly and to patient's left.

either to the left or right of the vertebral column. A right arch in itself causes relative minor disturbances though it has been known to press on the right main bronchus or one of its branches and has led to pathologic changes in the lung. Of greater importance than the position of the arch itself is the location of the ligamentum arteriosum (or patent ductus) which must connect the pulmonary artery with the first portion of the descending

aorta. In some instances the ligamentum may be a harmless structure because it lies anterior to, and to the right of, the trachea as it courses backward (Fig. 13). More commonly, the ligamentum arteriosum passes to the left of the trachea and then around behind the esophagus to reach the aorta, thus completing a "ring" which constricts the esophagus and especially the trachea (Fig. 6). If this ring is sufficiently large, the functions of the esophagus and trachea are not altered to any important degree, but if the ligament is taut, the space within the encircling structures is so small that the incarcerated esophagus and especially the trachea are greatly disturbed.

With this anomaly, symptoms can develop which are quite similar to those which are produced by a double aortic arch, but generally they are not quite so severe. As a rule, the onset of complaints is more apt to be delayed until a little later in life; (the average age of the double-arch patients was under 6 months, whereas most of those with a right arch and left ligamentum arteriosum were about a year older). There may be a crowing type of respiration, some intercostal and suprasternal retraction, possibly recurrent pulmonary infection, and occasionally some hesitation in swallowing. Respiratory symptoms tend to be aggravated during deglutition.

Films of the chest may show pulmonary infection if the patient is seen during the time of such a complication. There is a prominent shadow (the right arch) projecting from the right of the superior mediastinum (Fig. 5). During inspiration there may be incomplete aeration of the lungs, and during expiration there may be hyperaeration, indicative of an obstruction somewhere above the carina. Lateral films of the thorax, if correctly exposed, can outline the air-filled trachea; the upper portion of this is normal, whereas the lower segment is distinctly narrowed. Instillation of lipiodol into the trachea gives better visualization; there is a slight and rather elongated indentation of the right wall of the trachea (imposed by the adjacent aortic arch), indentation of the anterior surface of the trachea (where the pulmonary artery is pulled against it), and a depression on the left side of the trachea (from the ligamentum arteriosum). With a swallow of barium one finds (at the same level as the tracheal defects) that the esophagus has a narrow but deep constriction, especially on its left-lateral and posterior surfaces. Above this posterior notching of the esophagus, it is sometimes possible to identify a separate defect, passing obliquely upward and to the left, caused by the left subclavian artery which arises from the aorta and passes behind the esophagus to reach the left apex of the chest. By fluoroscope and simple film studies, it is usually possible to recognize accurately this combination of anomalies, but in some instances it has been almost impossible to differentiate this from a double aortic arch with a right descending aorta. If conclusive evidence is desired prior to operation, angiography will visualize the aortic pathway and can lead to a positive recognition of the type of pathology which actually exists. Such study in several cases has provided excellent delineation of the vascular structures, but from a practical standpoint angiography is seldom required because it is possible to recognize the esophageal and tracheal compression by more simple means and to proceed forthwith to surgical alleviation (the surgical approach being the same, regardless of the type of pathology).

Treatment of this condition is obviously one of alleviation and not of cure, because it is impossible to shift the aortic arch from its right-sided bed (Fig. 6C). Operation includes the identification, the liberation, and the division of the ligamentum arteriosum, so that the constricting "ring" is broken. When this is properly performed, the pulmonary artery falls forward into a more normal area and sufficient room is given for the esophagus and the trachea to drop backwards and to the left. Whenever the left subclavian artery is

found behind the esophagus, it should also be cut. This step (while not so important as the severance of the ligament) helps somewhat to release the constricting mechanism.

In undertakings of this sort, great care must be exercised in the recognition of all of the regional vessels so that the exact components of the anomalous situation are known before any structure is divided. It is possible to accomplish this by opening into the anterior mediastinum (after removal of the thymus) and also by entering the posterior mediastinum (behind the vagus nerve). It is difficult but important to identify the left recurrent laryngeal nerve, which takes off from the vagus, courses closely around beneath the ligamentum arteriosum and then proceeds upward, quite adherent to the esophagus. In all subjects it has been possible to find this nerve and leave it uninjured.

Seven patients have been operated upon with this anomaly, the youngest 2 months and the oldest 12 years of age; there have been no deaths. The first operation was performed April 12, 1948. The results in all subjects have been those of striking improvement. The children have shown complete disappearance of any pre-existing dysphagia and there has been marked alleviation of the respiratory distress which all had prior to operation. In the 12 year old child, repeat tracheograms at the end of a year showed rather disappointing growth of the tracheal rings in the involved area. While it is possible that this portion of the trachea can still grow until the time that the patient reaches maturity, this case emphasizes the desirability of carrying out operations much earlier in life, so that prompt removal of the external pressure will give the trachea the best possible chance to enlarge during the childhood years.

Roentgenologists and cardiologists have long recognized that a rather large number of patients possess a right aortic arch and have few symptoms therefrom. Presumably, these have had either a ligamentum arteriosum in front of the trachea (Fig. 13) or else the ligament has passed to the left of the trachea and has been very long and lax. There are many humans with a right aortic arch who do not require any operative intervention, but it is important to recognize those occasional individuals who have a high degree of tracheal narrowing, because it is in this group that surgical attack is a procedure of great value. If such surgery is undertaken, the best long-term results will probably follow those operations which are performed early in life, before the tracheal wall has been permanently deformed.

Anomalous Innominate Artery

The innominate artery can originate at a point farther along on the arch than normal; when it does so, it must wind around the anterior surface of the trachea as it courses upward and to the right to reach the right apex of the thorax (Figs. 7 and 8). If the vessel is long and flabby it will probably not give rise to important symptoms; conversely, a large and tight one can compress the trachea to a serious degree. While the pathology is seemingly only a minor variation from normal and would appear to be of little consequence, the severity of symptoms which can accompany it was emphasized by the first baby who came to the authors' attention. This 4 month old girl had been hospitalized elsewhere since birth because of dyspnea, inspiratory and expiratory crow of considerable degree, intercostal and suprasternal retraction, pallor, and on at least two occasions there had been frank pneumonia. At times the respiratory distress was marked enough to require the use of an oxygen tent, which on one occasion was employed for as long as two weeks. The baby had a marked tendency to hold the head in hyperextension—a position which apparently improved the exchange of air. When the head was forceably pushed forward in

direct alignment with the body, the exchange of air obviously diminished. When the head was further pushed forward by the examiner to a position of flexion, the exchange of air was completely shut off, though the respiratory motions continued and the struggling baby became fussy and apprehensive. In contrast, when the head was placed again in marked extension, the airway was improved. The child had no hesitancy in swallowing. The respiratory symptoms were not made worse by feeding.

By roentgenographic study, the esophagus is entirely normal. The aortic arch is normal

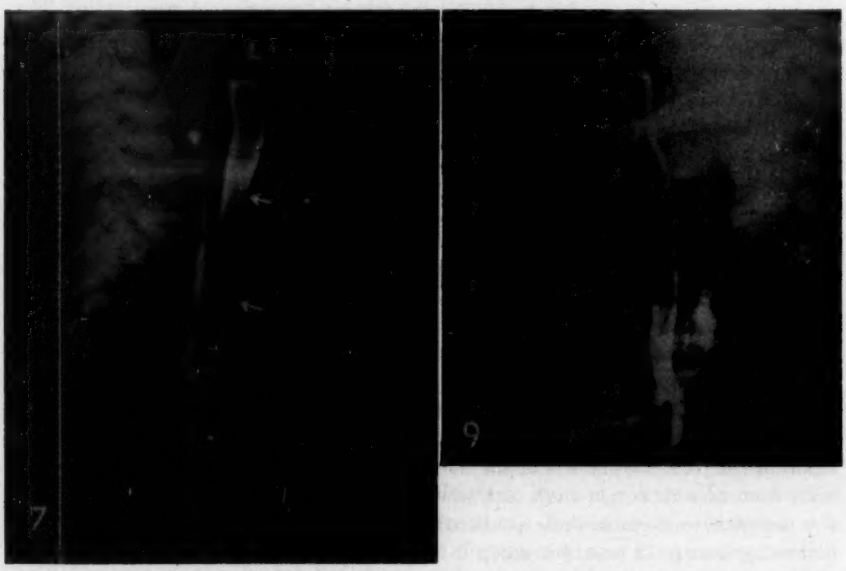

FIG. 7. Lateral RG from baby with deformity of anterior surface of trachea by anomalous innominate artery (compare Fig. 8). Posterior wall of trachea is normal, but anterior surface is markedly compressed between levels indicated by arrows. (Esophagus had been normal by barium studies.)

FIG. 9. Lateral RG from child with anterior compression of trachea by anomalous left common carotid artery (compare Fig. 10). Front border of trachea is indented between arrows. (Esophagus was normal by barium examination.)

in size and position. Films of the trachea (without contrast medium) may show little in the antero-posterior projection, but lateral views suggest a narrowing in its lower third. Visualization with lipiodol clearly indicates that the posterior surface of the trachea is normal, whereas the anterior one has a long and pronounced indentation, with rather ill-defined upper and lower limits. It may be exceedingly difficult or indeed impossible to determine whether the innominate artery or the left common carotid artery (described in the next section) is at fault, but in some instances the obliquity of the tracheal defect suggests one or the other. In the absence of any anterior, mediastinal shadow (such as cyst or neoplasm) a filling defect certainly suggests some abnormal blood vessel in the region. Any narrowing of a trachea which hints the presence of an abnormal blood vessel can also raise the question whether the diminished lumen is dependent upon incomplete development of the tracheal cartilages. Data on this point can be gathered by serial observa-

tions throughout the respiratory cycle. If the tracheal defect is due to some external pressure, it will remain fixed during the respiratory cycle, but if a defect is due to deficient cartilaginous rings the calibre of the trachea will diminish during expiration.

Upon exploration of the thorax it is possible to view this region clearly after dissecting off and discarding the thymus. The aortic arch is normal in size, position and direction. The vessels arising from it are not unusual, except for the fact that the innominate artery takes off from the arch a bit farther to the patient's left than is normal, indeed it is apt to

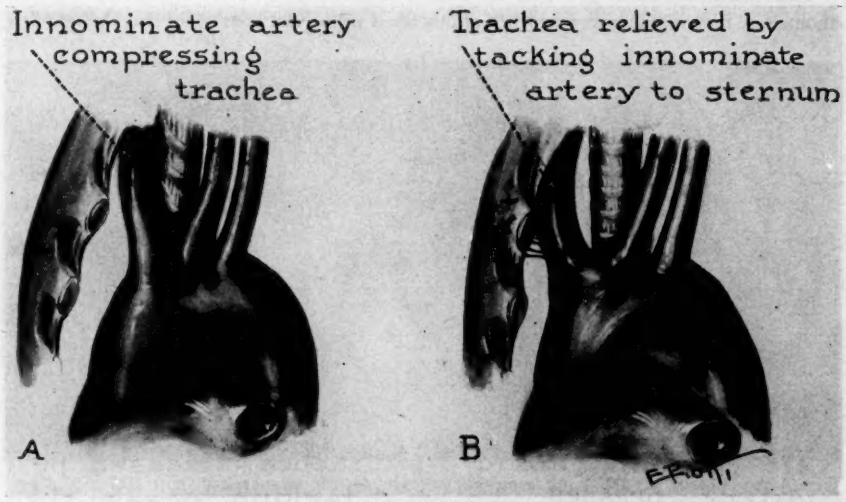

FIG. 8. Anomalous innominate artery which compresses front of trachea. Four patients with this condition have been treated. A. Anatomic peculiarity of innominate artery, in which vessel has origin from aortic arch farther to patient's left than normal. As it courses upward toward right apex of chest, vessel winds around and indents front of trachea. B. Surgical correction of condition by pulling vessel forward so that it no longer touches trachea.

have a common origin with the left carotid artery (Fig. 8). The vessel can be seen wrapped around the anterior surface of the trachea, giving a decided indentation of the same. While it might be possible to relieve quickly the respiratory distress by cutting the artery, such a step is so fraught with the danger of brain damage that it should never be done. The trachea can be freed of the oppressing vessel by dislocating the latter into a more anterior position. This can be accomplished with four or five silk sutures (00 or 000 Deknatel), grasping merely the adventitia, placing some of them well up toward the superior aspect of the vessel and others well down toward its base. These silks are then threaded onto large cutting needles which are thrust through the sternum at suitable points. Tightening and tying the mattress stitches at appropriate tension will draw the innominate artery forward so that it is completely lifted off of the trachea (Fig. 8B). These maneuvers are relatively easy to perform. The stitches must not enter the lumen of the vessel, nor indeed must they go far enough into the vessel wall to cause any damage thereto. Sufficient pull can be obtained by grasping only the adventitial structures and by distributing the pull through a number of stitches.

The results of this simple undertaking have been extremely gratifying. Four patients,

all under 1 year of age, have been operated upon, the initial operation being performed October 17, 1946. The first patient had previously been hospitalized for four months; she was discharged eight days after operation, completely relieved of symptoms. She has been well in every respect during the 3½ years since operation. The other three patients have been likewise fully cured of their respiratory complaints.

Anomalous Left Common Carotid Artery

This malformation is probably of considerable rarity. It is somewhat akin to the anomalous innominate artery which was described in the last section, in that the vessel is

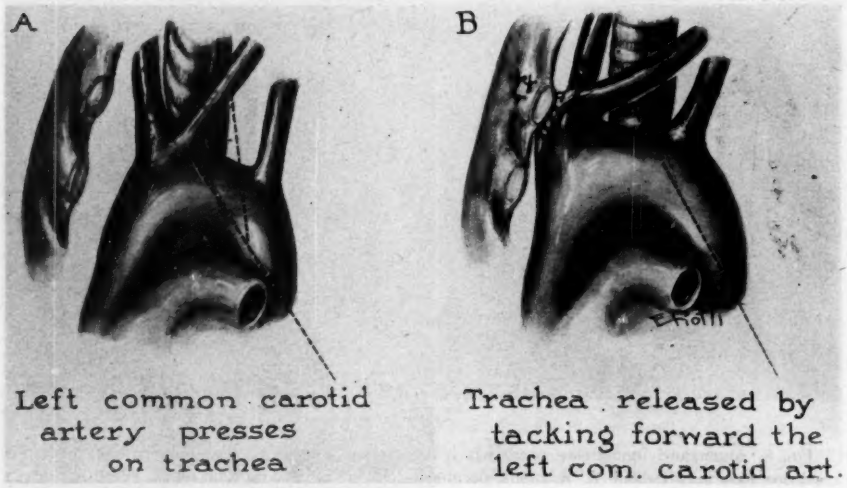

Fig. 10. Anomalous left carotid artery, compressing trachea. Two patients with this condition have been treated. A. Anatomic arrangements showing left common carotid artery with origin farther to patient's right than normal. To reach left apex of thorax, vessel winds around front of trachea and indents it. B. Surgical correction by dislocating left common carotid artery forward and thereby taking all pressure off trachea.

normal in size and distribution but has an origin which is slightly unusual (Fig. 10). It branches off of the aortic arch more to the patient's right than is customary; it must therefore wind around the anterior surface of the trachea as it courses upwards and to the left, to reach the left apex of the chest. The symptoms produced will obviously depend upon the degree of pressure which is exerted against the front of the trachea.

The authors have encountered two cases of this sort, in neither of which was there any disturbance in swallowing, but in both of which there was moderate respiratory distress, some crowing during respiratory movements, dyspnea of mild to moderate degree, and several bouts of pulmonary infection. These subjects were both under 1 year of age.

By roentgenographic examination, the findings are quite similar (Fig. 9) to those which have been described for an anomalous innominate artery. The esophagus is normal by barium study. The aortic arch is normal in size and position. The trachea has a posterior wall which is sharp, distinct, and of normal contour, whereas the anterior surface shows a rather long indentation or filling defect. (There is no anterior mediastinal cyst or

tumor to account for these changes.) Appropriate fluoroscopic or film studies taken at various angles might show that the defect is a grooved one, running upward and obliquely to the left, which finding strongly suggests that the indentation is due to an anomalous left common carotid artery. However, it may be difficult to see that such obliquity exists and hence the exact identification of the offending vessel may be impossible.

The surgical treatment of this condition (Fig. 10) is similar to that described for an anomalous innominate artery. The carotid impinges against the trachea and doubtless this pressure could be removed by severance of the vessel, but the high chance of cerebral

FIG. 11. RGs from patient with aberrant right subclavian artery (compare Fig. 12). A. Lateral view with barium swallow showing filling defect on posterior surface of esophagus, high in thorax. B. A-P view of oblique posterior esophageal defect. C. Oblique view of esophagus, showing winding defect caused by aberrant right subclavian artery. (There was no concomitant deformity of trachea.)

ischemia militates against such a step. A preferable therapy consists of pulling the carotid artery forward with mattress stitches which are anchored through the substance of the sternum; appropriate tension applied through such sutures can draw the vessel anteriorly so that it no longer has any contact with the trachea.

Two patients have been subjected to this procedure. The first operation was performed May 21, 1947. Both youngsters have had complete relief of respiratory distress.

ABERRANT SUBCLAVIAN ARTERY

"Dysphagia lusoria" has long been known to come from an aberrant subclavian artery (Fig. 12) which presses upon the esophagus, excellent descriptions of the clinical picture and the related pathology having been made by Bayford in 1794. Normally, the right subclavian branches from the innominate, but it is not uncommon for it to take off independently from the distal part of the aortic arch. It ascends and must deviate to the right to reach the right apex of the chest. In rare instances the artery has been described as passing in front of the trachea, in a higher percentage of cases it runs between the trachea and esophagus, but in the vast majority of subjects it courses behind the esophagus. In the series reported here there has been one patient who had a right aortic arch but with no constriction from a ligamentum arteriosum (Fig. 13), the ligament being in front of

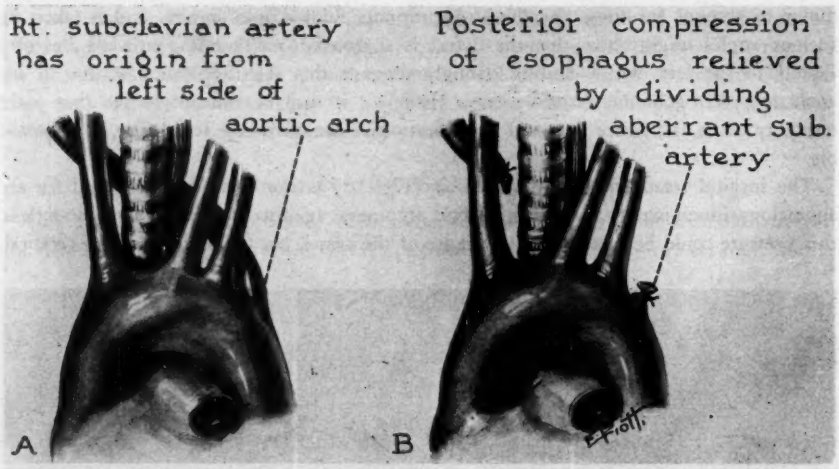
Rt. subclavian artery has origin from left side of aortic arch
A
Posterior compression of esophagus relieved by dividing aberrant sub. artery
B

FIG. 12. Aberrant right subclavian artery. Ten patients with this anomaly have been treated. A. Anatomic arrangement. Instead of arising from innominate artery, right subclavian branches from distal part of aortic arch and runs behind esophagus, upward and toward patient's right. B. Surgical correction of condition, by double ligation and division of subclavian.

and to the right of the trachea, but there was hesitancy in swallowing because a left subclavian artery ran upward and to the left, behind the esophagus.

Aberrant right subclavian arteries have been recognized frequently by radiologists who have seen them during the esophageal portion of gastrointestinal examinations; in a very

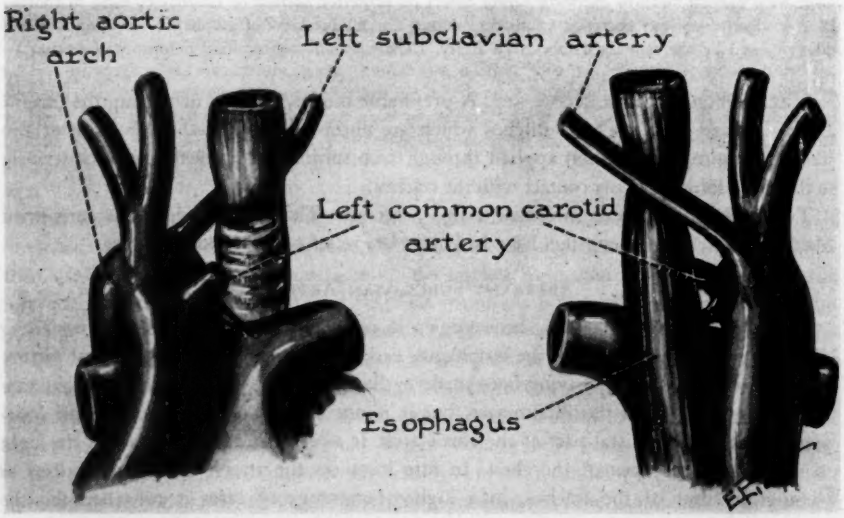

FIG. 13. Rare anomaly with right aortic arch, harmless ligamentum arteriosum in front of trachea and constricting left subclavian artery running up behind esophagus. One patient with dysphagia has been treated by division of this left subclavian artery.

high percentage of these subjects there have been no important disturbances in the swallowing mechanism. However, in a few humans the subclavian artery can stretch sufficiently taut around the esophagus so that the peristaltic wave in the latter is altered and the patient experiences a hesitation in swallowing which may be bothersome and annoying. In babies, delay in swallowing can be found even in the early months of life. The child is hungry and eager for food, will suckle, and start to swallow in an apparently normal way but will then have difficulty in getting the bolus started along the esophageal pathway. Some of the food or milk might pass downward, while the remainder stays in the pharynx for a considerable length of time, or is expectorated. Some of these patients have no delay in swallowing milk or other fluids, but they encounter difficulties when solid or semisolid food is added to the diet. Conversely, there have been several instances in which solid food was taken with alacrity but fluids were taken only with hesitation. This disturbed swallowing is not accompanied by manifestations of pain, but a young child or baby obviously has some sort of distress; after several attempts of swallowing there may be temporary refusal to try it again. The amount of food or milk taken at any one sitting might be relatively small, but as a rule the general nourishment of the individual does not suffer, because the mother usually learns that a sufficient intake over a 24 hour period can be attained by giving the feedings in small amounts and offering them frequently. These children have no respiratory distress between feedings, but there may be some aspiration of material while attempting to swallow, so that gurgling or noisy respirations appear at such times.

By roentgenologic examination the abnormality can be identified quickly and with a high degree of accuracy (Fig. 11). The aortic arch is normal in size, position and direction. The trachea shows no abnormality, and indeed in most cases the absence of respiratory symptoms does not lead to a detailed examination of the airway. With a swallow of barium, the lateral projection reveals a defect of rather small calibre on the posterior wall of the esophagus at the level of the third or fourth thoracic vertebra. On antero-posterior view, this indentation runs obliquely upward and toward the patient's right, the direction and position of the defect being in a line from the distal part of the aortic arch to the right apex of the chest. There is usually little or no ballooning of the esophagus above this area, but a delay in the passage of the barium is commonly observed.

The surgical undertaking for the alleviation of dysphagia lusoria is a rather simple one (Fig. 12); it consists merely of exploration of the posterior mediastinum, freeing the anomalous subclavian artery from its bed, doubly ligating and dividing it. There need be no hesitancy about severing the first part of a subclavian artery because there is sufficient supply through collateral channels to the second and third portions of the vessel to give an adequate flow of blood to the corresponding arm.

In this series of 11 surgically treated cases, there were 10 with an aberrant right subclavian (Fig. 12) and one with the offending vessel on the left (Fig. 13). These patients varied in age from 3 weeks to 6 years. The first operation was performed November 26, 1945. All subjects survived this surgery, and in each instance there was complete disappearance of the symptoms which had existed prior to the undertaking.

Technical Considerations of Operation

It is not pertinent to list here the details of operative steps, but some general statements might be of value for those who are interested in the technical aspects of these surgical endeavors.

If pulmonary infection is present, as is so frequently the case in the first four types of anomalies just described, adequate preoperative management should include control of this before undertaking surgery. Appropriate chemotherapy, administration of oxygen as required, and the use of a steam room in some cases, are important elements in preoperative care.

For the administration of fluids or blood which might be required from time to time, it is wise to insert a cannula or a plastic catheter into an ankle vein. Such a precaution becomes a great asset during operation because it facilitates the intravenous injection of fluids, which under some circumstances might have to be given quickly. Furthermore, the inlying vein catheter provides an extremely useful avenue for supplying nourishing fluids during the early postoperative period.

Anesthesia in all these subjects has been with a closed system, using ether or cyclopropane. In all cases, an intratracheal tube, preferably of soft polyethylene, has been employed. Such a tube is essential for the maintenance of an adequate airway, particularly in the first four types of anomalies just described, in each of which the trachea is markedly narrowed and an adequate exchange might not be obtained until a tube is passed down beyond the obstructed point.

In all these cases, regardless of the type of vascular anomaly which is contemplated, the operative attack has been through a left antero-lateral incision with a transpleural approach. The incision is made below the breast, the chest is entered throughout the length of the third interspace, and the third and second costal cartilages are severed. The left lung is temporarily collapsed during operation, and is expanded immediately thereafter. This approach gives an admirable view of the superior mediastinum from its left, lateral aspect. While it is possible that a right-sided opening might be satisfactory for some of the anomalies, a thorough consideration of the various problems leads to the firm conviction that it is better to expose all these malformations from the left side. In the first four types of anomalies described (double aortic arch, right arch with left ligament, anomalous innominate artery, anomalous left common carotid artery), the anterior mediastinum must be opened and structures liberated in an adequate fashion so that all the important vessels can be viewed, palpated and accurately identified. To accomplish this, the thymus gland can be readily dissected from its bed (after opening the parietal pleura) carrying the dissection upward and avoiding the innominate veins; about three-quarters to seven-eighths of the thymus can be cut off and discarded. This removal can be completed without perforating the right pleural sac. With some types of anomaly, such as a double arch or a right arch with a left ligament, it is necessary to make a separate opening into the posterior mediastinum to identify structures in that region. This is done by incising the parietal pleura parallel to and behind the vagus nerve, dislocating this nerve forward so that it is left uninjured. The posterior mediastinal exploration can be carried to the mid-line and even to the right of the vertebral column. This dissection must be made slowly, carefully, and with due concern for the tragedy that would result from damage to any of the large vessels which could give uncontrollable hemorrhage. In all cases (where posterior mediastinum dissection has been necessary) the thoracic duct has been identified and left undisturbed.

In those cases where operation is performed for division of an aberrant subclavian artery, no entry is required into the anterior mediastinum, but the posterior mediastinum is entered through a longitudinal incision behind the vagus nerve. With this opening, it is possible to dissect down behind the aortic arch, to identify the subclavian, and to divide it.

Great emphasis must be laid upon the fact that constrictions of the esophagus and trachea are not caused solely by the vessels or ligaments which compress them, but that the constriction is likewise produced by fibrous bands or sheaths which accompany these vessels and ligaments. Hence it is important to divide not only the appropriate vessel or ligament, but it is likewise essential to cut any strands or bands of tissue which accompany them; failure to do so will give only partial release of an incarcerated esophagus or trachea.

Following completion of the mediastinal portion of one of these procedures, the chest wall is closed tightly, and all air is aspirated from the pleural cavity with a catheter which is then withdrawn just before the skin is sutured. It has never been found necessary to tap the chest following operation; in some instances small amounts of pleural fluid have accumulated which subsequently disappeared spontaneously.

For those children who have had division of a subclavian artery, no special treatment is necessary following operation; fluids can be swallowed as soon as there is recovery from anesthesia. In all the other malformations, there has been a pre-existing tracheal obstruction, there has been manipulation of the trachea during mediastinal exploration, and there has been some trauma to the interior of the trachea from the intratracheal tube. In all these cases, close postoperative supervision for 48 to 72 hours is essential. Appropriate chemotherapy is given to control any infection which might be lurking in the respiratory tract. Oxygen is administered to most patients for several days. It has been customary to place the subjects in a room or small compartment with a very moist atmosphere (produced by constant nebulization of water into the enclosure) because of its beneficial effects in reducing any irritation which is present in the glottis, larynx or trachea. Beyond the first few days, fluids and milk can be offered as tolerated and can be rapidly increased in amount to supply adequate caloric and fluid intake. Hospitalization has seldom run beyond 8 or 10 days following operation.

Summary

Description is given of five different types of anomalies of the great vessels in the superior mediastinum which can produce compression of the esophagus or trachea (or both). These malformations of the vascular system can give rise to difficulties in swallowing and to serious disturbances in pulmonary ventilation. These anomalies include double aortic arch, right aortic arch with a left ligamentum arteriosum, anomalous innominate artery, anomalous left common carotid artery, and an aberrant subclavian artery.

The various symptom complexes which can be found with these anomalies are described. Endoscopic visualization of the interior of the esophagus or trachea gives valuable information in some cases. The investigation of these subjects should include fluoroscopic and film studies of the esophagus and trachea by contrast media. Data gathered from such roentgenologic examinations usually give a fairly clear idea of the type of vascular anomaly which is present.

It is possible to attack surgically each of these vascular malformations. In general, the esophagus or trachea can be relieved by division of an anomalous vessel or by displacement of an artery in such a manner that it is carried away from the compressed structure. When necessary, these operative procedures can be undertaken in very young babies, even in the presence of a high degree of respiratory obstruction. All the operations have been through a left anterolateral, transpleural approach, under general anesthesia with a closed system. The results of operation in 40 patients are analyzed.

It is evident that many vascular anomalies in the thorax which disturb the functions of the esophagus or trachea can now be treated with an excellent chance of relieving the obstructive symptoms.

SPANISH ABSTRACT

La Compresion de la Traquea y del Esofago por Anomalias Vasculares Tratamiento Quirurgico en 40 Casos

Se describen cinco diferentes tipos de anomalias de los grandes vasos del mediastino superior, las cuales pueden producir la compresion del esofago o de la traquea o de ambos organos conjuntamente. Estas malformaciones del sistema vascular pueden producir dificultades en la deglución y serias alteraciones en la ventilacion pulmonar. Estas anomalias incluyen: el cayado aortico doble, el cayado aortico derecho con ligamento arterioso izquierdo, anomalias de la arteria innominada, presencia anomala de la arteria carotida izquierda comun, y arteria subclavia aberrante.

Los distintos cuadros clinicos que pueden encontrarse con estas anomalias con descritos. La visualizacion endoscopica del interior del esofago y de la traquea puede arrojar un informacion valuable en algunas areas. Se sugiere el uso de el examen fluroscopico y radiografico con placas seriadas del esofago y traquea usando medio de contraste, en la investigacion de estos pacientes. Las observaciones obtenidas con estos examines radiologicos, generalmente dan una idea clara del tipo de anomalia vascular presente.

Los autores consideran posible el tratamiento quirurgico de todas estas anomalias vasculares. En general, la obstrucción del esofago o de la traquea puede ser abolida madiante la division del vaso sanguíneo anomalo o a veces con la separacion o desplazamiento de la arteria en manera tal que esta (la arteria) es llevada lejos de la estructura comprimida. Si es necesario, estos procederes operatorios pueden llevarse a cabo en recién nacidos, aún con gran obstruccion respiratoria. Todas las operaciones fueron realizadas a traves de una incision antero-lateral izquierda transpleural, con anestesia general de sistema cerrado. Los autores analizan los resultados de la operacion en 40 casos.

Es evidente que muchas anomalias vasculares del torax que alteran las funciones normales de la traquea y del esofago pueden ser tratadas quirurgicamente con una excelente oportunidad de abolir los sintomas obstructivos.

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MEAT IN THE DIET OF PREMATURE INFANTS

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I. INTRODUCTION

MILK usually constitutes the main element in the diet of infants for the first six months or more of life although the number of foods available for infant feeding has steadily increased during the past 20 or 30 years, and formulae have been improved by altering the milk and adding various carbohydrates and fats. Strained meats are now available as an added source of protein, fat and minerals and as a substitute for milk for babies of all ages.

It has been stated by Kraybill[1] that meat supplies in adequate quantity all the amino acids necessary for infant growth, and that meat can, therefore, be used as a substitute for milk protein at all ages. Glaser[2] in 1944 described the successful use of homogenized and strained meat in the formulae of three infants with eczema who were allergic to milk, and cites the use of meat in the feeding of allergic infants by others as early as 1931.[3] Sanford and Campbell[4] in 1941 described the feeding in formulae of vacuum-dried defatted ground round steak to premature and full term infants 1 to 3 months old. The extra iron supplied by this supplement maintained the red blood cell count and hemoglobin levels of premature infants as well as did iron ammonium citrate in the usual dosage, but they found no difference in the blood picture of the meat-fed and control full term infants during the 6 to 12 month period in which they were followed. Leverton and Clark,[5] in 1947, reported the addition of strained meats to the formulae of 6 week old infants whose blood pictures were followed through eight weeks of meat feeding.

The protein metabolism of premature and other infants has been extensively studied by Levine and his associates, and reported in a long series of papers dealing with various aspects of metabolism in infancy. Healthy premature and full term infants are always in positive nitrogen balance once weight gain is established, and the balances are considerably higher in premature infants because of their more rapid growth. The average premature infant shows a positive balance of 0.3 gm. of nitrogen/kg./24 hours and retains about 50% of his nitrogen intake according to Levine.[6] He recommends that the daily protein allowances in the first month of life for infants weighing less than 2000 gm. be 4.4 to 6.0 gm./kg./day, and that this be 17% of the caloric intake. For premature infants 1 to 4 months of age and for full term infants, he recommends a protein allowance of 3.3 to 4.0 gm./kg./day, constituting 13% of the calories in the diet. Intakes above these levels are wasteful since a high percentage of the protein will be used for energy instead of storage and tissue anabolism.

Proteins are generally classified in nutritional studies according to their biologic value.

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In his chapter in *Proteins and Amino Acids in Nutrition,* Levine makes the following statement:[7] "The biological value of a protein in turn largely depends on its amino acid composition and is graded by the ratio of body weight gained to protein consumed or more reliably by the ratio of body protein gain (nitrogen balance) to protein absorbed." Analyses have shown that all the indispensable amino acids are present in meat in liberal quantities, and meat proteins have been found to be almost completely digestible, the range being from 90 to 100%.[1] A comparison of the amino acid composition of milk (whole cow's milk) and meat (lean) demonstrates that they are very much alike, meat being appreciably lower only in leucine and phenylalanine.[1] The exact amount of each essential amino acid necessary for adequate growth in the infant is unknown, but both cow's milk and meat do contain all the essential ones in high enough concentration to produce adequate growth if the protein requirements previously recommended are met. In infants the biologic value of proteins cannot be determined, but the adequacy of the protein intake is judged by following the nitrogen balance, the rate of body weight gain and the level of the blood proteins. It has been reported that the total blood proteins of the premature infant at birth are about 5.6 gm./100 cc. compared to a level of 6.4 gm. in the full term infant.[8] Because of his rapid growth and poor fat absorption, the premature infant requires higher protein intakes to provide enough for both energy requirements and growth.

Gordon and his associates[9] in 1937 reported a study of protein metabolism in premature and full term infants receiving human or cow's milk formulae. In addition to the nitrogen balance in gm./kg./24 hours, they reported the percentage of nitrogen intake that was absorbed, the percentage of intake retained, and the percentage of absorbed N which was retained (per cent utilized). These authors concluded that as the protein intake is increased, the nitrogen balance increases, but that conversely the per cent utilization decreases. There is, then, in infants a level of maximum efficiency for protein utilization similar to that which has been noted in studying the biologic values of proteins in rats where it is possible to vary the protein intakes more widely but keep other variables at a minimum.

Albanese and his associates[10] have shown that meat hydrolysates as a source of protein may be favorably compared with milk protein in biologic utilization. In a group of infants on isocaloric diets of equivalent protein content they found that the nutritional quality of cow's milk and the meat hydrolysate were equal. Although beef protein contains less phenylalanine and leucine than milk protein, nitrogen retention and body weight gains were the same on the two types of diet.

The present study was undertaken to evaluate the use of strained meats in the diet of premature infants. Balance studies of N, fat, calcium, phosphorus and iron were carried out, and additional observations on the clinical condition, weight and growth changes, the number and character of the stools, and hemoglobin and total serum protein levels of the infants were made.

II. Methods of Study

Clinical Methods

Subjects: The infants used as subjects for these studies are divided into 3 groups (table 1). Group I includes 11 healthy male premature infants upon whom N, fat and mineral balances were determined. Group II consists of 3 healthy premature infants, 2 males and 1 female, who were fed diets similar to those of the subjects in Group I, but on whom only stool collections were made

because of the difficulty in securing complete urine collections; and, therefore, only the fat absorption was studied. Group III contains 5 healthy male premature infants, 3 of whom received test diets containing only meat and olive oil as sources of protein and fat. The other 2 infants in this group were studied only on the control milk diets. Nitrogen fat and mineral balances were determined on this group of infants.

Regardless of the infant's age or birth weight, the experimental work was usually started when the infant weighed between 1700 and 2000 gm., was in good health, and had been gaining steadily for several days on the regular premature diet. The infants were selected for study as they became available, and the 6 different meats used were prescribed in the diets at random regardless of weight, age, race or any other factor in the infant's history. Female infants were not used in the nitrogen

TABLE 1

DIVISION OF SUBJECTS INTO GROUPS SHOWING DIET FED AND TYPE OF STUDY CARRIED OUT ON EACH GROUP

Group	No. of Subjects	Type of Subject	Type of Diet	Type of Study Carried Out
I	11	Premature Male Infants Each subject his own control	Milk	N, Fat, and Mineral Balances
	11		Meat-Milk	
II	1	Premature Female Infant	Meat-Milk	Fat Absorption
	2	Premature Male Infants	Meat-Milk	Fat Absorption
III	4	Premature Male Infants	Milk	N, Fat, and Mineral Balances
	3		Meat	

and mineral balance studies. The birth weights varied from 1000 to 2250 gm. The age at the time of study varied from 12 to 50 days.

Environmental Conditions: All the subjects were cared for in the premature nursery of the Pediatric Service and, when possible, special nurses were employed. Without a metabolism ward and specially trained personnel adequate control of all factors was impossible, and there were periods of known loss of specimens and errors in preparation of the diet which had to be considered in evaluating the data. The amount of refused formula was measured and the regurgitated formula estimated and deducted from the day's intake, but no correction was made for the small amounts of formula adhering to the bottle and nipple or about the mouth, though this has been found by others to amount to a 4% loss.[11] The infants were kept in an environment of constant humidity (45-50%) and temperature (27° C.) at all times. They were weighed daily to the nearest 5 gm.

Collection of Samples: For the subjects in Groups I and III the method of collection used was a modification of the method of Hoag[12] for collection of stools and urine in male infants, and a method used at the Boston Children's Hospital as observed by one of the authors. Each 24 hr. urine specimen was kept separately, but the daily stool specimens were pooled into 2 to 4 day specimens, depending on the length of the collection period. The stools were not marked at the beginning of each period, but adequate foreperiods on each diet were allowed. For the 3 subjects in Group II the stools were scraped from the diapers, and pooled into periods of 2 or more days.

Diets: The customary diet for premature infants in this institution is a half-skimmed milk formula (Alacta) with 10% weight/volume of cane sugar added, and the control formulae for this study had about the same total caloric value and a similar per cent distribution of calories from fat, protein and carbohydrate as the half-skimmed milk. For the infants in Group I and II the test formulae containing milk and meat were isocaloric with the control cow's milk diets and contained the same proportion of fat and protein. The diets for the infants in Group III were isocaloric with the other 2 types of diet and had the same per cent distribution of calories but contained no milk.

Because the metabolism of the premature infant approaches that of the full term infant as he grows older, the control collection period preceded the meat period in some subjects and in others the order was reversed to eliminate variations due to increasing age and weight of the subjects. Each collection period was preceded by a foreperiod of 2 or more days on the diet to be studied. The diets were ordered from the hospital formula room and were calculated in advance to specifications based on the weight the infant was expected to gain during the collection period, provided the established daily gain continued. The meat diets for Group III were prepared by one of the authors. Daily representative samples of the formulae prepared and fed during the collection days were analyzed in the laboratory. The caloric intake was calculated to approximately 130-140 cal./kg., with 16-17% of the calories from protein and 20-23% from fat. When meat protein was substituted for some of the milk protein in the test diets, it was added in sufficient quantity to provide one-third of the dietary protein. This quantity, which was about 30 gm./day for most of the infants, was selected because it was noted that adding meat in any greater proportion would mean lowering the calcium intake below a level satisfactory for adequate calcium retention. A commercial preparation of strained and cooked meats, including veal, pork, lamb, beef, calf heart and liver, was used.* Each subject received only 1 type of meat throughout his period of study.

In order to be able to vary both the amount of milk protein and milk fat in the diets but keep the per cent of fat and protein constant when meat was added, it was necessary to use a mixture of dried milk preparations rather than a liquid half-skimmed milk. The 2 types used in various proportions were whole powdered milk and a dried half-skimmed milk preparation. Since the fat content of the meats was low compared even to half-skimmed milk, it will be readily understood that when meat was added a greater proportion of whole powdered milk, of high fat content, was used in order to keep the percentage of fat at the same level as in a half-skimmed milk formula. The remaining calories were always added as cane sugar.

The diets containing no milk (Group III) were modifications of those used by McQuarrie[18] in an investigation of allergic infants. These were composed of meat, olive oil, calcium gluconate, sodium monohydrogen phosphate, potassium dihydrogen phosphate, cane sugar and water. They were isocaloric with the control formulae, with the same percentage composition, and were prepared by one of the authors to insure a minimum of error.

The diets on the whole were quite acceptable to the infants, who seldom regurgitated any feeding. No gastrointestinal disturbances occurred, but it was noted that the stools were softer in consistency for the 1st 1 or 2 days that the infants were on the meat diets. All infants were given about 5,000 units of vitamin A and 1,000 units of vitamin D as navitol® with viosterol® and 50 mg. of ascorbic acid daily, or approximately the same unitage in the form of vi-penta® drops.

Additional Observations: In addition to the collection of urine and stool samples, observations were made on the clinical condition of all infants during their hospital stay. Records were kept of the history of both mother and infant, and when possible the infants were seen at monthly intervals after discharge whether the meat supplement was continued or not. Measurement of the body length, and head and chest circumferences were made at birth and at intervals during the period of observation. Laboratory studies included hemoglobin and total protein determinations made on capillary blood. A record was kept of the number, color and consistency of the stools during the infant's hospital stay.

Calculations: The data are presented as obtained but not treated statistically because of variations which could not be controlled. The intake of each infant was recorded in cubic centimeters for each 24 hr. period, and these daily intakes averaged to obtain the average intake for the entire collection period. In cases where the intake for 1 or more days was grossly under the usual intake, the data for those days were omitted. The caloric intake was calculated on the basis of the analyzed protein content of the formulae, and the calculated fat and carbohydrate content, using the constants 4, 9 and 4. Where there is a marked discrepancy between the calculated and analyzed protein content, there is an error in using the calculated value for the fat intake. This was taken into consideration in analyzing the results, and the fat absorption data for these subjects omitted from the tables. The values for the intake of Ca, P and Fe are all based on the analyses of the formulae and the average daily intake for the period.

* Supplied by Swift and Company, Chicago.

The fat absorption represents the intake minus the fecal excretion given in gm./kg. body weight/24 hr. The nitrogen balance is calculated as the intake minus the sum of the fecal and urinary excretion in grams of N/kg. body weight/24 hr. A calculation was also made of the per cent of the ingested N which was absorbed, the per cent of ingested N which was retained and the per cent of absorbed N which was retained (per cent utilization). Since the nitrogen intakes vary over a range of 0.648 to 1.054 gm./kg./24 hr., the balance and the per cent utilization are not strictly comparable. All the intakes provided sufficient protein to produce positive balances and satisfactory weight gain. The Fe, P and Ca balances are calculated as the intake minus the output in gm./kg./24 hr. The output represents the combined fecal and urinary excretion for Ca and P and fecal excretion alone for Fe. On a few subjects studied the urea, ammonia, creatine and creatinine components of the urine were separately estimated. The figures obtained were similar to those found in the literature both on the control and meat diets, and these analyses were not carried out on the rest of the subjects.

Laboratory Methods

Preliminary treatment of urine and fecal samples: The 24 hr. urine specimens, collected under toluene, were refrigerated until time for individual analysis in triplicate.

The 24 hr. stool specimens, which represented the composite of the individual stools collected in the presence of a small amount of alcoholic thymol solution at each feeding period (every 3 hr.), were weighed, pooled and mixed. Aliquots of the samples were taken by weight for analysis of N in triplicate. A single large sample served for fat analysis, and another large single sample served for moisture determinations and, after dry ashing, for mineral analysis.

Preliminary treatment of diets: Each day the diet kitchen made up the ordered diets in a quantity twice the infant's requirement. One half of this diet was subjected to terminal pasteurization, and the other half sent to the chemical laboratory. The formulae for each day were pooled and mixed, and proper aliquots were taken by volume for analysis of N and minerals. The fat intake was calculated from the determined fat contents of the ordered dietary constituents.

Determination of moisture content of stools: Stool samples (25 to 50 gm.) were weighed into tared porcelain crucibles and dried at 110°C. for 24 hr. The water content was calculated from the weight loss on drying.

Determination of the calcium, phosphorus and iron contents of stools: The stool sample, previously dried at 110°C., was ashed over a Meeker burner with final heating in a muffle furnace at 500-550° C. The resulting ash was dissolved in sufficient 1:3 HCl to effect solution and filtered into a 100 ml. volumetric flask using Whatman #40 filter paper. Reashing of the filter paper was carried out when necessary. Glass-distilled water was used to bring the final volume to 100 ml.

The analysis for Fe was made on suitable aliquots by the colorimetric method of Hummel and Willard[14] using an Evelyn colorimeter.

Calcium analysis was carried out by the titrimetric method of Kochakian and Fox using ammonium hexanitratocerate.[15]

Phosphorus was determined by the colorimetric method of Fiske and Subbarow[16] using an Evelyn colorimeter.

Determination of fecal fat: An aliquot (25-50 gm.) of each stool sample was weighed in a Soxhlet thimble and subjected to extraction with 95% methanol for 24 hr. During this process concentrated HCl was added intermittently to decompose any soaps present. At the end of a 12 hr. period fresh methanol was added to the Soxhlet extractor. Following methanol extraction a 24 hr. ether extraction was carried out in two 12 hr. periods. The methanol extracts were pooled and concentrated upon the steam bath. This extract was dissolved in ether in a separatory funnel to which was added the ether extracts, and the total extractable lipid in the ether phase was washed 3 times with water. The ether solution, free of HCl, was dried over anhydrous sodium sulfate, filtered, and the ether removed on the steam bath. The extracted fecal lipids were transferred to a tared 100 ml. round bottom flask for final weighing. The extractable lipid was calculated on the basis of original wet weight of total stools.

Determination of the nitrogen content of stools and urine: Aliquots of each 24 hr. urine specimen (5 ml.) and 1 gm. aliquots of total stool samples were digested with concentrated sulphuric acid in the presence of selenium catalyst and anhydrous potassium sulfate. Distillation of ammonia was carried

out with Hengar apparatus and the distillate collected in saturated boric acid solution. Titration of the solutions was carried out to an end-point determined by a Beckman pH meter.

Determination of calcium and phosphorus content of urine: The urinary excretion of Ca and P was determined in triplicate upon one or two 24 hr. urine samples if a 3 day metabolism study was made and upon 2 of the 24 hr. urine specimens if a 4 day metabolism study was made.

Calcium was determined in triplicate upon 15 ml. aliquots of urine by the method of Kochakian and Fox.[35]

Phosphorus was determined by titration with uranyl acetate solution according to the directions outlined in Peters and Van Slyke.[37]

Determination of hemoglobin and total serum proteins: Hemoglobin values were determined by the acid hematin method using a Klett-Summerson colorimeter or by the Sahli method, and the total serum proteins were determined by the refractometric method using the conversion table of Utheim.[38]

III. Protein Metabolism

Results

The nitrogen balance data are presented in detail in table 2. A summary of these results is given in table 3 and chart 1, which also includes a summary of values secured by

TABLE 2

Detailed Results of Nitrogen Absorption and Utilization, and Weight Gains of Premature Infants Fed Milk, Meat-Milk, and Meat Diets

SUBJECT	AVERAGE WEIGHT GMS.	AGE DAYS	LENGTH FORE PERIOD	LENGTH COLLECTION PERIOD	AVERAGE DAILY WEIGHT GAIN	TOTAL CALORIES PER KG. PER 24 HRS.	DIETARY NITROGEN GMS. PER KG. PER 24 HRS.	URINE NITROGEN GMS. PER KG. PER 24 HRS.	RANGE OF URINE NITROGEN	STOOL NITROGEN GM. PER KG.	TOTAL NITROGEN EXCRETION GMS. PER KG. PER 24 HRS.	NITROGEN RETAINED GMS. PER KG. PER 24 HRS.	N RETAINED ——— X 100 N INTAKE	N RETAINED ——— X 100 N ABSORBED	N ABSORBED ——— X 100 N INTAKE
													%	%	%
GROUP I MILK (CONTROL) DIET															
CH	[illegible]	24	3	3	27	155	0.838	0.337	[illegible]	0.139	0.476	0.362	43.2	80.4	51.6
MA	1835	12	3	3	33	132	0.887	0.834	0.808–0.911	0.187	0.981	0.360	38.8	43.1	91.7
WI	1950	36	4	4	34	134	0.697	0.499	0.411–0.599	0.202	0.701	0.338	48.8	87.0	85.0
ME	1980	24	3	3	24	143	0.875	0.696	0.706–0.689	0.131	0.827	0.486	55.1	54.4	92.4
SE	2095	25	4	3	45	113	0.888	0.442	0.421–0.490	0.084	0.525	0.390	83.9	81.1	88.5
MA	2040	41	6	3	46	142	0.832	0.782	0.682–0.813	0.214	1.000	0.371	63.5	48.0	87.4
SM	2075	12	4	3	29	142	0.888	0.937	0.892–0.982	0.118	1.079	0.388	40.9	43.8	93.3
MA	2170	20	3	3	30	145	0.818	0.738	0.690–0.844	0.192	0.930	0.388	47.6	83.4	89.2
RIB	2310	48	4	3	49	127	0.893	0.815	0.698–0.920	0.168	0.983	0.487	53.3	58.8	91.9
DE	2445	29	3	3	36	129	0.787	0.703	0.670–0.868	0.197	0.900	0.389	51.4	87.8	89.1
RH	2490	31	3	3	42	134	0.923	0.703	0.695–0.874	0.189	0.891	0.984	63.3	87.0	94.4
GROUP I MEAT-MILK DIET															
ME	1845	17	3	2	21	138	0.827	0.523	0.500–0.547	0.189	0.882	0.388	48.2	84.1	88.4
MA	1964	13	3	4	11	132	0.648	0.643	0.600–0.649	0.208	0.811	0.184	27.4	33.8	78.3
RIB	2015	41	6	3	29	136	1.054	0.720	0.704–0.710	0.288	1.008	0.833	37.4	80.7	84.1
CH	2030	31	2	4	41	153	1.044	0.603	0.444–0.580	0.339	0.942	0.580	55.3	68.1	84.1
RA	2065	19	3	4	27	131	0.818	0.729	0.778–0.685	0.173	0.902	0.381	46.8	58.0	90.9
DE	2155	21	8	4	32	137	0.850	0.624	0.638–0.614	0.333	0.957	0.404	47.8	59.0	88.9
SE	2180	32	4	3	7	125	0.780	0.684	0.682–0.904	0.221	0.770	0.370	48.8	84.0	87.4
WI	2240	46	3	2	8	139	0.840	0.890	0.706–0.681	0.321	1.211	0.629	33.8	48.9	88.9
RH	2245	24	4	4	43	128	0.833	0.742	0.673–0.879	0.158	0.900	0.433	52.0	58.7	91.3
MA	2250	48	4	3	20	134	0.798	0.920	0.878–0.985	0.255	1.175	0.277	34.8	40.4	86.8
SM	2345	21	6	5	38	132	0.777	0.734	0.892–0.589	0.250	0.984	0.388	49.2	53.8	89.2
GROUP III MILK (CONTROL) DIET															
FR	2020	50	7	3	29	140	0.943	0.493	0.488–0.598	0.223	0.716	0.388	68.3	84.7	93.6
SP	2080	15	5	4	37	128	0.812	0.683	0.744–0.598	0.180	0.863	0.481	61.9	86.9	91.1
GA	2345	20	3	3	14	135	0.858	0.690	0.783–0.868	0.119	0.809	0.814	84.8	93.8	94.1
BA	2620	35	3	3	20	134	0.904	1.020	———	0.190	1.210	0.444	44.8	53.3	91.9
GROUP III MEAT DIET															
BA	2440	27	16	5	20	120	0.786	0.568	0.770–0.307	0.308	0.986	0.408	50.8	83.8	80.0
YA	2450	25	8	4	23	120	0.788	0.576	0.548–0.609	0.448	0.718	0.488	58.1	81.4	77.0
GA	2520	28	5	3	33	139	0.893	0.549	0.781–0.318	0.280	0.909	0.333	38.8	87.4	87.8

Gordon and his associates[9] on the nitrogen metabolism of five premature infants fed human and cow's milk formulae of varying protein content.

Retention and per cent utilization: The average dietary nitrogen intake of the 11 infants in Group I when on the meat-milk diet was 0.841 gm./kg. This was 0.027 gm./kg. greater than their intake when on the control diet (0.814 gm./kg.). When the infants were fed the control milk diet, the average nitrogen retention was 0.413 gm./kg. A slightly lower value of 0.384 gm./kg. was obtained for the same infants fed the meat-

TABLE 3

SUMMARY OF RESULTS OF NITROGEN BALANCE STUDIES INCLUDING FIGURES FROM LITERATURE FOR COMPARISON

Diet	No. of subjects	Av. wt. gm.	Av. age in days at beginning of study	Av. wt. gain during fore-period and collection period	Dietary N gm./kg.	N Retained gm./kg.	Utilization $\frac{N_2 \text{ Retained}}{N_2 \text{ Absorbed}}$ %	$\frac{N_2 \text{ Retained}}{N_2 \text{ Intake}}$ %	$\frac{N_2 \text{ Absorbed}}{N_2 \text{ Intake}}$ %
Milk	11	2105	27	35.5	0.814	0.413	55.9	50.7	90.6
Meat-Milk	11	2121	28	24.9	0.841	0.384	53.3	45.6	86.0
Milk	4	2266	30	25.0	0.880	0.488	60.7	55.4	91.4
Meat	3	2470	26	25.6	0.825	0.478	70.3	57.9	82.2
Cow's Milk*	5	2507	33		0.773	0.352	50.9		

* Gordon et al.[9]

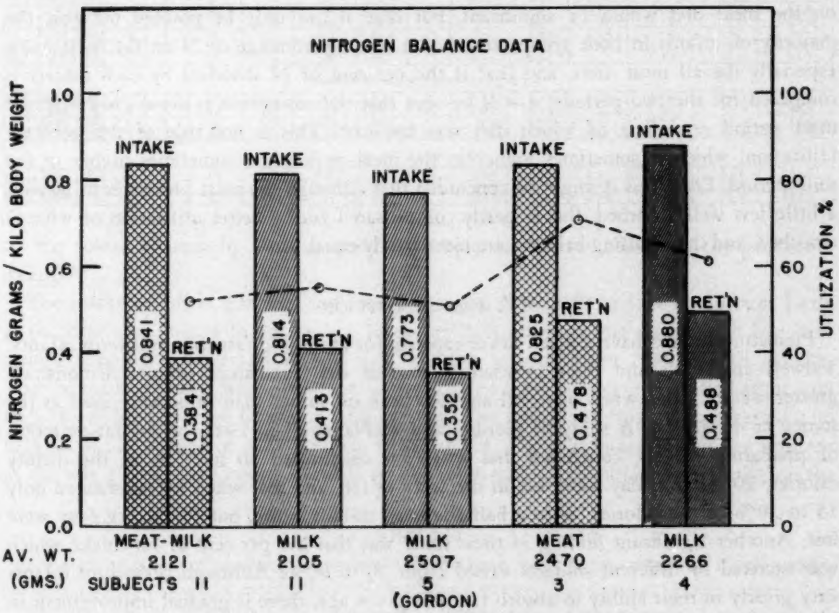

CHART 1. Graph showing comparison of nitrogen intakes and retentions with per cent of N utilized by premature infants fed isocaloric cow's milk, meat and milk, and meat formulas with equivalent protein content. Vertical columns represent nitrogen intake and nitrogen retention in gm./kg./24 hr. and broken line per cent of N utilized. Figures from literature shown for comparison are from Gordon et al.[9]

milk combination. The percentage of retention was correspondingly lower (5.1%) in this group.

Utilization of N was likewise lower on the test formulae (2.6%) but not significantly so. A comparison with the figures published by Gordon and his co-workers (table 3) shows that all values are within a close range. The range of retention of N for the meat

periods is greater than for the milk periods, largely because of the poor intake of one subject, Ma.

A comparison of the values obtained from three infants fed test diets containing only meat protein shows a 9.6% higher per cent utilization than when they and a fourth control infant were fed the milk diet. Nitrogen retentions were almost equal despite the higher dietary nitrogen intakes during the control collection periods. The series is too small to make the difference in per cent utilization of significance.

Absorption of nitrogen: The average absorption of dietary N expressed in per cent and designated the "coefficient of apparent digestibility" was 90.6% for the all-milk formulae, and 86.0 for the meat-milk formulae fed the subjects in Group I. The absorption of N appears to be reduced when meat is added to the diets, but the difference, 4.6%, is not significant for this series. In comparing the per cent absorptions of the four infants in Group III, the coefficient of digestibility of meat alone was 82.2%, and of milk as the control formulae, 91.4%. In a larger series this difference of 9.2% less N absorbed on the meat diet would be significant, but here it can only be pointed out that the majority of infants in both groups absorbed a lower percentage of N on the meat diets, especially the all meat diets, and that if the per cent of N absorbed by each subject is compared for the two periods, it will be seen that the absorption is always lower in the meat period regardless of which diet was fed first. This is not true of the per cent utilization, which is sometimes higher in the meat period and sometimes higher in the milk period. From this it might be concluded that although the meat protein is in general a little less well absorbed, this is partly compensated for by better utilization of what is absorbed, and the resulting balances are more nearly equal.

IV. Fat Absorption

Premature infants have a much lower capacity for absorbing fats than full term infants. Tidwell and Holt and their associates[19] showed that premature infants demonstrate greater weight gains when olive oil and soy bean oil rather than milk were used as the source of dietary fat. A study by Gordon and McNamara[20] in 1941, on the fat excretion of premature infants, concluded that when fat constituted 30 to 55% of the dietary calories, 20 cal./kg./day were lost in the feces as fat; and that when fat constituted only 15 to 20% of the calories, as in a half-skimmed milk mixture, but 10 cal./kg./day were lost. Another significant finding in their study was that the per cent of fat intake which was excreted by different subjects varied from 20 to 80%. Although premature infants vary greatly in their ability to absorb fats at a given age, there is gradual improvement in this ability with increasing age.

Fat absorption studies were carried out on the subjects in Group III and on nine of the subjects in Group I, both on the control diets and on the meat-milk diets. The three infants in Group II were studied only on the meat-milk diets. On these three infants the stools were collected by scraping the diapers and moisture determinations were not made. The clinical and laboratory methods used in the fat absorption studies were otherwise the same as those described in Part II.

Results

The fat absorption data for Groups I, II and III are shown in detail in table 4, and a summary of these results appears in table 5 and chart 2 which also contain a summary

TABLE 4

DETAILED RESULTS OF FAT ABSORPTION STUDIES ON PREMATURE INFANTS FED MILK, MEAT-MILK, AND MEAT DIETS INCLUDING NUMBER OF STOOLS, MOISTURE CONTENT OF STOOLS, AND PER CENT DRY WEIGHT OF STOOLS AS FAT

SUBJECT	AVERAGE WEIGHT GMS	AGE DAYS	LENGTH FORE PERIOD	LENGTH COLLECTION PERIOD	AVERAGE DAILY WEIGHT GAIN GMS	TOTAL CALORIES PER 24 HRS.	TOTAL CALORIES PER KG. PER 24 HRS.	CALORIES AS FAT	NO. STOOLS	MOISTURE CONTENT STOOLS	FAT INTAKE GMS. PER KG. PER 24 HRS.	FAT EXCRETION GMS. PER KG. PER 24 HRS.	FAT ABSORB. GMS. PER KG. PER 24 HRS.	COEFFICIENT OF DIGESTABILITY %	DRY WEIGHT OF STOOLS AS FAT %
GROUP I MILK (CONTROL) DIET															
GH	1812	24	2	3	27	287	155	34.7	3	82.6	3.88	1.67	2.21	57.0	79.5
RA	1855	12	3	3	33	247	132	28.0	4	81.4	3.10	0.58	2.52	81.3	35.7
ME	1980	24	3	3	24	292	145	33.7	3	93.1	3.51	0.74	2.77	78.9	51.4
SE	2035	25	4	3	45	337	115	25.0	4	76.2	2.80	0.88	1.82	65.0	72.7
RIA	2060	41	6	3	46	294	142	32.8	3	82.4	3.83	1.60	2.03	54.0	82.3
SM	2075	12	4	3	25	292	142	32.5	3	78.2	3.55	1.27	2.28	64.3	76.7
RIB	2310	48	4	3	49	293	127	26.1	2	81.2	2.94	0.86	2.08	70.7	90.5
DE	2445	29	5	3	36	316	129	28.5	3	82.7	3.12	1.20	1.92	61.5	58.5
RH	2450	31	3	3	42	329	134	34.9	3	84.7	3.98	0.73	3.15	81.2	53.9
GROUPS I & II MEAT-MILK DIET															
ME	1845	17	3	2	21	256	138	30.2	3	80.8	3.24	1.26	1.98	61.1	63.0
RIB	2017	41	6	3	29	274	136	30.3	4	81.6	3.37	1.31	2.06	61.2	67.9
CH	2030	31	2	4	41	314	153	33.4	3	83.3	3.94	2.31	1.63	41.4	70.3
BA	2098	19	3	4	27	281	136	29.0	3	79.7	3.20	0.67	2.53	79.1	47.1
KA	2160	20	7	4	45	317	147	25.9	4	—	2.90	0.91	1.99	68.7	—
DE	2158	21	8	4	32	277	137	19.8	2	84.3	2.18	1.18	1.00	46.0	91.8
SE	2180	32	4	3	7	280	128	29.0	5	85.6	3.20	1.50	1.70	53.2	77.2
RH	2245	24	4	4	43	277	126	22.5	3	85.5	2.40	0.73	1.67	69.5	57.6
RIA	2250	48	4	3	20	303	134	29.9	3	77.4	3.32	1.56	1.76	53.0	84.3
LE	2275	14	5	3	32	301	132	22.9	5	—	2.52	1.04	1.48	58.7	—
NI	2290	18	2	2	30	320	140	24.4	4	—	2.72	0.59	2.13	78.3	—
SW	2345	21	6	5	35	310	132	26.7	3	81.4	2.98	1.13	1.85	61.8	58.8
GROUP III MILK (CONTROL) DIET															
FR	2010	80	7	3	29	282	140	31.3	2	79.2	3.48	1.24	2.24	64.5	57.9
SP	2090	18	5	4	37	267	128	29.3	5	74.2	2.96	1.62	1.34	45.3	87.5
GA	2248	80	5	3	14	316	135	29.3	2	79.6	3.09	0.25	2.84	92.0	24.4
BA	2420	38	3	3	20	351	134	30.9	2	82.3	3.42	0.63	2.78	81.5	35.6
GROUP III MEAT DIET															
BA	2440	27	18	5	20	293	120	24.4	3	84.6	2.69	0.61	2.08	81.4	32.5
TA	2480	28	8	4	23	293	120	24.2	3	85.9	2.68	0.83	1.85	69.0	43.7
GA	2820	28	8	2	33	348	139	29.5	2	75.0	3.28	0.76	2.52	76.8	86.2

of the values secured by Gordon and McNamara on the fat absorption of premature infants.[20]

The intake of fat in gm./kg. body weight ranged from 2.18 to 3.94 for Groups I and II on meat and milk with an average intake of 2.98 gm./kg. The control diet for these groups supplied an average of 3.37 gm./kg. fat, ranging from 2.80 to 3.88 gm./kg. The fat intake for the three infants in Group III fed meat and olive oil varied from 2.68 to 3.28, with an average intake of 2.89 gm./kg. The controls of this group ingested 2.96 to 3.48 or an average of 3.25 gm./kg. body weight. The percentage of calories ingested as fat was 19.8% for Groups I and II on the meat-milk combination, and 22.6% on the

TABLE 5

SUMMARY OF RESULTS OF FAT ABSORPTION WITH FIGURES FROM LITERATURE FOR COMPARISON

Diet	No. of subjects	Average wt. gm.	Fat intake gm./kg./24 hr.	Fat excretion gm./kg./24 hr.	Coefficient of digestibility
Milk	9	2116	3.37	1.06	68.7
Milk-meat	12	2155	2.98	1.18	60.4
Milk	4	2266	3.25	0.89	72.3
Meat	3	2470	2.89	0.74	74.4
½ Skim milk*	11	2125	2.05	0.86	58.0
Olive oil*	8	2201	2.06	1.01	50.9

* Gordon and McNamara.[20]

control milk diet. The subjects in Group III had a 20.6% caloric fat intake on meat and olive oil and 22.4% when on milk alone.

The average fat excretions for the different types of diet varied from 0.74 to 1.18 gm./kg., which is the same range as those reported by Gordon and McNamara. The individual values ranged from 0.58 to 1.67 gm./kg. for the subjects in Groups I and II on milk, and from 0.59 to 2.31 gm./kg. for these groups on meat-milk diets. For Group III on milk the range was 0.25 to 1.62, and on meat and olive oil it was 0.61 to 0.83 gm./kg.

The per cent absorbed or the coefficient of apparent digestibility was greatest for the

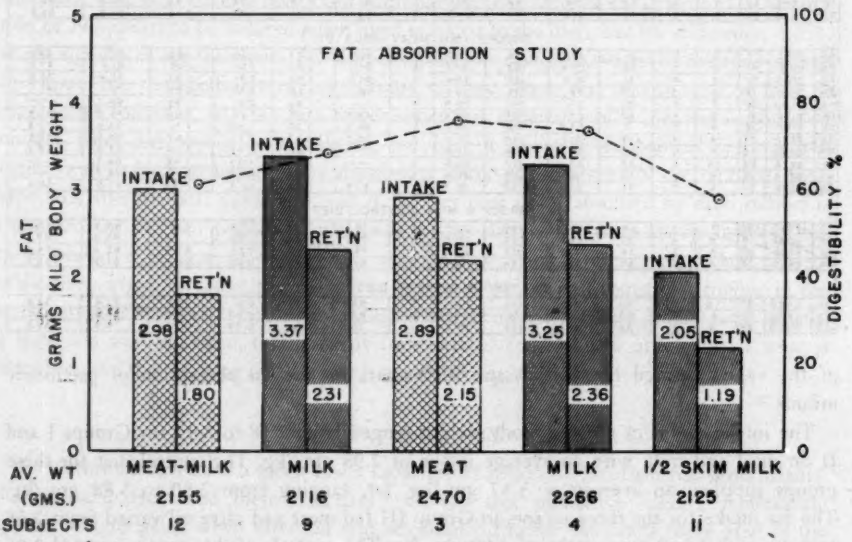

CHART 2. Graph showing fat intakes and retentions of premature infants fed isocaloric cow's milk, milk and meat, and meat formulas with equal fat content. Vertical columns represent fat intake and fat retention and broken line indicates per cent of fat absorbed. Figures from literature for comparison are from Gordon et al.[9]

meat-olive oil period of Group II, and least for the meat-milk period of Groups I and II. The digestibility of fat was 8.3% greater on the control diets for Groups I and II than on the meat-milk diets, but the infants in Group III showed a 2.1% greater fat digestibility when fed meat and olive oil than when on milk alone. Again it should also be noted that if each subject is compared with himself for the two periods, the per cent absorbed was always greater in the control period regardless of which period came first. This may be entirely due to the fact that the fat intake was always slightly higher in the control periods, and the series is too small and variable to draw any conclusions either on the basis of the averages or the individual figures. The retentions are comparable to those shown in the figures for comparison in table 5 and chart 2 for premature infants on low fat intakes reported by Gordon and McNamara[20] who found the loss of calories as fecal fat was approximately 10 cal./kg. for their subjects fed half-skimmed milk mixtures. In the present study the loss of fecal fat expressed in cal./kg. body weight was

10.7 calories for Group I and II when on the meat substitution diet, and 9.7 calories for Group I on the control diet. For the smaller number of infants in Group III, the loss was 6.6 cal./kg. when fed meat and olive oil alone, compared to 8.7 cal./kg. when on the control diet.

V. Mineral Metabolism

The metabolisms of Ca and P are closely related; the retentions of each are in direct proportion to the amounts ingested. A high phosphorus intake may decrease the calcium retention, whereas a high calcium intake causes loss of vitamin D. Benjamin, Gordon and Marples[21] have stated that, "Premature infants present no defect in their ability to retain calcium and phosphorus, for they retain more when they are given more, and they retain more proportionately than do full-term infants with a similar diet, e.g., cow's milk plus vitamin D." Where the absorption of fat is poor and there is an associated poverty in the absorption of vitamin D, the retention of Ca may be limited. Much of the Ca ingested is lost in the feces in the form of insoluble compounds such as calcium phosphate, calcium carbonate and, at times, calcium soaps. Holt[22] estimates that less than half the Ca is usually absorbed and others have said that bottle-fed infants retain only 30 to 50% of the calcium and phosphorus intake, and the breast-fed infant 50 to 70%.[23] These figures are misleading unless it is recalled that the actual amounts of intake and retention show that cow's milk, not human milk, is better utilized in this respect by the premature infant, probably because the lack of adequate P in human milk limits the retention of Ca. Von Sydow,[24] in a study on the development of rickets in premature infants, concludes, "The phosphorus requirement of the premature infant is not satisfied when only human milk is given; and the calcium requirement only if vitamin D is supplied. . . . A supply of cow's milk may fulfill the phosphorus requirement, but not the calcium requirement if no vitamin D is supplied." There are a number of factors which influence the absorption such as the presence of phosphate ions which form insoluble salts with Ca, and low acidity in the upper portion of the small bowel which increases the tendency to form these salts. But the presence of vitamin D is probably the most important factor and permits adequate absorption even over a wide range of intake.

The effect of varying the calcium-phosphorus ratio, and the difference in the absorption of Ca and P derived from different foodstuffs is less well understood. Full-term infants on cow's milk formulae with calcium-phosphorus ratios of 1.26 show good absorption if vitamin D is supplied. An infant born four weeks before term has only half as much Ca as he would have at term, and needs a greater supply of Ca to continue his rapid deposition. Benjamin, Gordon and Marples,[21] in a study of the calcium and phosphorus requirement of premature infants, found that on cow's milk formulae with an average intake of 165 mg. of Ca/kg. body weight, 114 mg. or an average of 70% was retained; and 67 mg./kg. or 61% of a phosphorus intake of 109 mg./kg. was retained. Holt and others[22] have suggested that another factor which may affect the calcium retention in premature infants is the level of fat in the diet. On a high fat diet a greater amount of Ca is lost in combination with the unabsorbed fat as soaps. Premature infants usually show good retentions of Ca on cow's milk formulae. Fairbanks and Mitchell[25] have suggested that the bones of premature infants may be highly unsaturated with Ca, thereby favoring its rapid deposition from the blood.

If meat is used as a substitute for milk in infant feeding, it is necessary to supplement the diet with Ca and P in some other form. There is 10 times as much P as Ca in meat,

TABLE 6

DETAILED RESULTS OF CALCIUM, PHOSPHORUS AND IRON BALANCE STUDIES ON PREMATURE INFANTS FED MILK, MEAT-MILK, AND MEAT DIETS

			CALCIUM MG. PER KG. PER 24 HRS.				PHOSPHORUS MG. PER KG. PER 24 HRS.					IRON MG. PER KG. PER 24 HRS.		
SUBJECT	AVERAGE WEIGHT GMS.	AGE DAYS	INTAKE	EXCRETION URINE	EXCRETION FECES	RETENTION	INTAKE	EXCRETION URINE	EXCRETION FECES	RETENTION	CA/P RATIO	INTAKE	FECAL EXCRETION	BALANCE
GROUP I MILK (CONTROL) DIET														
CH	1812	24	214	2	119	93	148	53	22	73	1.27	0.138	0.111	+ 0.027
RA	1855	12	207	2	142	63	—	—	—	—	—	0.133	0.282	− 0.127
WI	1950	36	191	0	151	40	132	80	35	17	2.35	0.118	0.189	− 0.081
ME	1980	24	223	1	111	111	150	59	28	63	1.76	0.096	0.081	+ 0.015
SE	2055	25	144	4	65	75	—	—	—	—	—	—	0.112	—
RIA	2060	41	253	2	177	74	153	91	34	28	2.64	0.112	0.083	+ 0.029
SM	2075	12	221	3	141	77	141	65	32	44	1.75	0.092	0.048	+ 0.043
MA	2170	20	230	5	190	35	139	75	33	31	1.13	0.138	0.088	+ 0.050
RIB	2310	48	230	3	140	87	120	70	30	20	4.35	0.074	0.074	0.000
DE	2445	29	177	2	125	50	125	57	33	35	1.43	0.066	0.102	− 0.036
RH	2450	31	220	2	89	129	162	55	20	87	1.48	0.090	0.102	− 0.012
GROUP I MEAT-MILK DIET														
ME	1845	17	154	1	102	51	123	52	15	56	0.91	0.590	0.130	+ 0.460
MA	1964	13	112	4	102	6	102	64	20	18	0.33	0.473	0.036	+ 0.437
RIB	2015	41	188	3	98	87	134	69	7	58	1.67	0.268	0.104	+ 0.164
CH	2030	31	175	4	90	81	141	67	16	58	1.40	0.720	0.286	+ 0.434
RA	2065	19	151	4	86	61	—	—	—	—	—	0.387	0.244	+ 0.143
DE	2155	21	137	3	98	36	100	61	24	15	2.40	0.306	0.139	+ 0.167
SE	2180	38	137	4	77	56	—	—	—	—	—	—	0.129	—
WI	2240	46	154	1	86	67	136	71	13	52	1.29	0.640	0.412	+ 0.228
RH	2245	24	133	3	65	65	102	51	12	39	1.67	0.312	0.183	+ 0.129
RIA	2250	48	181	3	87	91	90	82	8	0	—	0.205	0.022	+ 0.183
SM	2345	21	139	4	86	49	102	52	12	38	1.29	0.290	0.094	+ 0.196
GROUP III MILK (CONTROL) DIET														
FR	2020	50	210	2	121	87	162	52	20	90	0.97	0.070	0.045	+ 0.025
SP	2080	15	194	1	134	59	149	51	23	75	0.79	0.067	0.120	− 0.053
GA	2345	20	244	6	120	118	130	64	30	36	3.28	0.029	0.029	0.000
BA	2620	35	214	4	135	75	104	68	9	27	2.78	0.024	0.019	+ 0.005
GROUP III MEAT-OLIVE OIL DIET														
BA	2440	27	277	1	112	164	127	74	38	15	10.9	0.247	0.098	+ 0.149
TA	2450	22	274	2	108	164	122	41	11	70	2.3	0.248	0.114	+ 0.134
GA	2520	28	266	6	59	201	127	102	9	16	12.6	0.818	0.397	+ 0.421

TABLE 7

SUMMARY OF RESULTS OF CALCIUM BALANCE STUDIES INCLUDING FIGURES FROM LITERATURE FOR COMPARISON

Diet	No. of subjects	Average wt. gm.	Average age days	Intake mg./kg./ 24 hr.	Urine excretion mg./kg./ 24 hr.	Fecal excretion mg./kg./ 24 hr.	Retention mg./kg./ 24 hr.
Milk	11	2105	27	210	2	132	76
Meat-milk	11	2121	29	151	3	89	59
Milk	4	2266	30	216	3	128	85
Meat	3	2470	26	272	3	93	176
Cow's Milk* (Olac ®)	3	2449	25	165			114

* Benjamin et al.[21]

but still the quantity of meat supplying as much protein as the usual milk formula would give only half the amount of P which constitutes an adequate intake, and therefore only one twentieth of the necessary Ca. No attempt was made to regulate the calcium and phosphorus intakes of the subjects on any of the diets except for those three infants who

received the meat-olive oil diet. Their mineral requirements were covered by the addition of calcium gluconate and primary and secondary phosphates. As has been noted, the substitution of meat in Groups I and II was held at one third of the daily protein requirement because any greater substitution would have reduced the calcium and phosphorus intakes below the level recommended for good retentions.

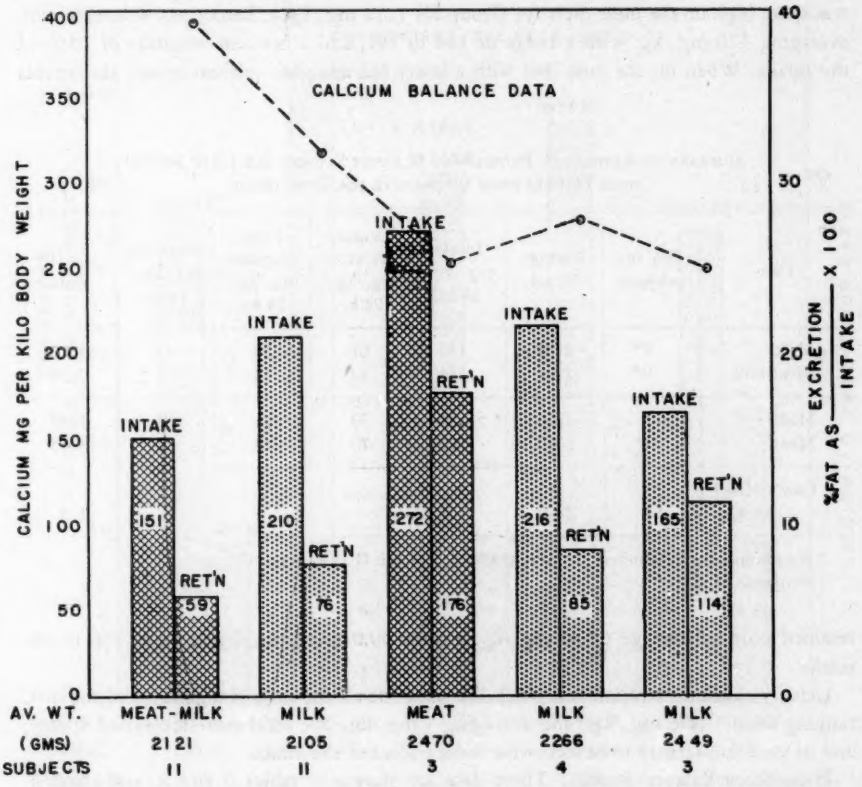

CHART 3. Graph with vertical columns showing calcium intakes and retentions of premature infants fed isocaloric cow's milk, milk and meat, and meat formulas of variable calcium content. Broken line indicates per cent of fat intake excreted. Last column shows figures from literature for comparison from Benjamin et al.[21]

The subjects for the mineral metabolism study are the male premature infants of Groups I and III. The clinical and laboratory methods appear in Section II of this paper.

Calcium Balance Results: All mineral balance data appear in detail in table 6 and summaries of the calcium balances appear in table 7 and chart 3. The average intake of Ca for Group I on the meat-milk diet was 151 mg./kg./day with a range of 112 to 188 mg./kg. On the control milk diet the average intake was 210 mg./kg. with a range of 177 to 253. The retentions for the meat-milk period were lower than on the milk periods, averaging 59 mg./kg. (range 6.0 to 91.0 mg./kg.) as compared to an average

retention on the control diet of 76.0 mg./kg. (range 35.0 to 111.0 mg./kg.). On both diets the percentage retention was poor; 39.1% for the meat-milk combination, and 36.1% for the control milk formulae. This does not compare too favorably with an average per cent retention of 69.1% reported by Benjamin and her associates.[21]

Because no alteration was made in the mineral content of McQuarrie's formula[13] when it was modified by the authors for feeding premature infants, the calcium intake was quite high on the meat diets for Group III (272 mg./kg.). Retentions were excellent, averaging 176 mg./kg. with a range of 164 to 201, and a per cent retention of 65% of the intake. When on the milk diet with a lower but adequate calcium intake, the infants

TABLE 8

SUMMARY OF RESULTS OF PHOSPHORUS BALANCE STUDIES AND Ca/P RATIOS WITH FIGURES FROM LITERATURE FOR COMPARISON

Diet	No. of subjects	Average wt. gm.	Intake mg./kg./ 24 hr.	Urinary excretion mg./kg./ 24 hr.	Fecal excretion mg./kg./ 24 hr.	Retention mg./kg./ 24 hr.	Ca/P Ratio
Milk	9*	2139	141	67	30	44	1.73
Meat-milk	9*	2121	114	63	14	37	1.59
Milk	3	2266	134	59	21	54	1.57
Meat	4	2470	122	70	18	34	5.18
Cow's Milk† (Olac ®)	3	2449	109			63	1.8

* No phosphorus determinations were made on 2 of the 11 subjects in Group I.
† Benjamin et al.[21]

retained only an average of 85 mg./kg. (range 59.0-118.0 mg./kg.), or 39.3% of the intake.

Urinary calcium excretion was much the same for all the infants regardless of the diet, ranging from 1 to 6 mg./kg., and averaging 3 mg./kg. The fecal excretion varied widely, and its variation seemed to be somewhat independent of the intake.

Phosphorus Balance Results: These data are shown in tables 6 and 8, and chart 4. The subjects reported are nine of the infants in Group I and those in Group III.

Phosphorus intakes were adequate for each type of diet, with a fairly narrow range (100.0 to 162.0 mg./kg. body weight), but the retentions were low and do not compare well with the results of Benjamin and her co-workers.[21] The average retentions were greater on the control diets in both groups than on the meat diets. The retentions ranged from 0.0 (approximately) to 58 mg./kg. for Group I on the meat diet, and 17.0 to 87.0 on the control diet. For Group III the range was 15.0 to 70.0 mg./kg. on meat and olive oil, and 27.0 to 90.0 on the control diet.

The ratios of retention of Ca to P were above the minimum of 1.26:1 reported by other investigators. The ratio for the infants on the total-meat substitution diet was quite high 5.2:1. Although the retentions of Ca and P were not as high as expected, they are higher than those reported for premature infants fed human milk, and the subjects showed no

clinical evidence of hypocalcemia even though the meat-milk diets provided less Ca than would ordinarily be considered desirable for a premature infant.

Iron Balance Results: In both full term and premature infants the blood hemoglobin level drops for the first 2 to 3 months, but the hemoglobin of the premature infant usually falls more rapidly and to a lower level. The average full term infant seems to have

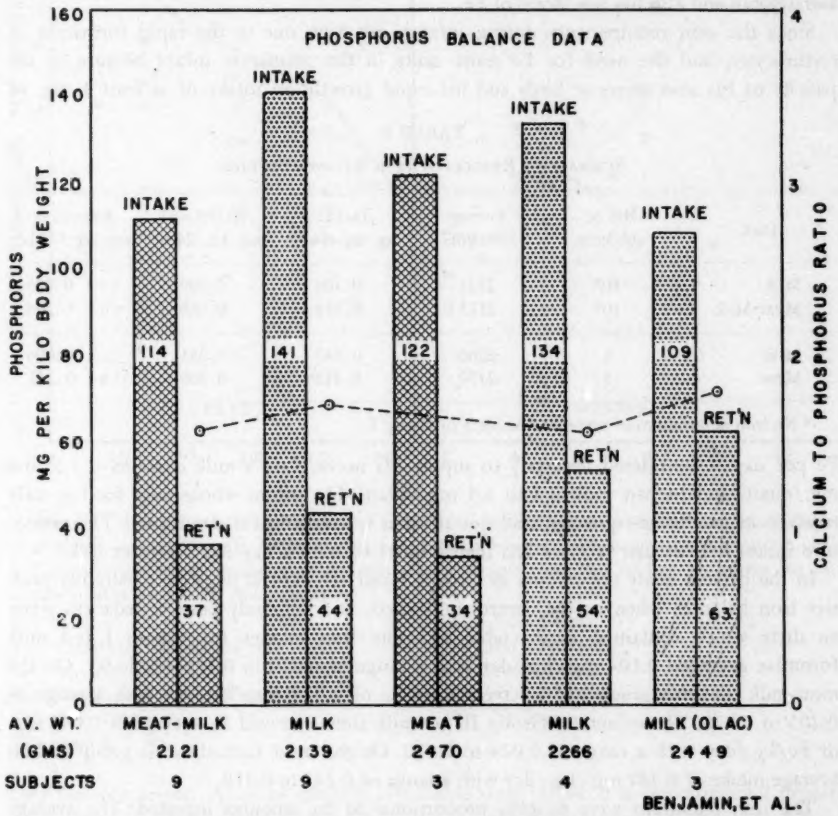

CHART 4. Graph showing phosphorus intakes and retentions and Ca/P ratios of premature infants fed isocaloric cow's milk, meat and milk, and meat formulas with variable phosphorus content. Vertical columns represent phosphorus intake and retention and broken line Ca/P ratio. Figures from literature for comparison are from Benjamin et al.[21]

adequate stores for the first six months of life during which time the iron intake is rather low. From then on the hemoglobin will rise if a mixed diet is fed, but will fall if only milk is given. The premature infant, on the other hand, frequently continues to be anemic throughout the first year of life, even on a mixed diet.

Merritt and Davidson[26] in 1943 reported on a group of premature and full term infants, studied with and without supplementary iron. The untreated premature infants showed a hemoglobin of 11.0 gm. in the second month, and the level remained at a low

point up to the age of 12 months. Those premature infants who received the iron supplement showed a rise in their hemoglobins to 14.0 gm. by the sixth month, demonstrating that the low point was transitory in those who received the iron supplement. The full term infants had a fall in hemoglobin to only 13.0 gm. by the second month. These authors concluded that the premature infant shows an exaggerated physiologic drop in hemoglobin and also has low stores of Fe.

Since the iron requirements during infancy are high due to the rapid formation of erythrocytes, and the need for Fe more acute in the premature infant because of the paucity of his iron stores at birth and his rapid growth, an intake of at least 1 mg. of

TABLE 9

SUMMARY OF RESULTS OF IRON BALANCE STUDIES

Diet	No. of subjects	Average wt. gm.	Intake mg./kg./24 hr.	Excretion mg./kg./24 hr.	Retention mg./kg./24 hr.
Milk	10*	2111	0.104	0.109	(−) 0.005
Meat-Milk	10*	2115	0.414	0.166	(+) 0.248
Milk	4	2266	0.045	0.051	(−) 0.006
Meat	3	2470	0.442	0.205	(+) 0.237

* No iron determination made on 1 subject in Group I.

Fe per day is considered necessary to supply his needs. Cow's milk contains 0.5 to 0.6 mg./quart, and human milk 0.4 to 1.4 mg./quart. The infant whose only food is milk receives an insufficient quantity, and not all of it is available for absorption. The premature infant who at first receives less than a quart of milk a day has a greater lack.

In the present study the infants in Groups I and III showed negative or slightly positive iron balances when on the control milk diets, and definitely positive balances when on diets which contained meat (table 6). The iron intakes for Group I fed milk formulae averaged 0.104 mg./kg./day with a range of 0.074 to 0.138 (table 9). On the meat-milk diet this group had an average intake of 0.414 mg./kg./day with a range of 0.205 to 0.720. The infants in Group III on milk alone received an average of 0.045 mg. of Fe/kg./day with a range of 0.024 to 0.070. On the meat formulae this group had an average intake of 0.442 mg./kg./day with a range of 0.247 to 0.818.

The iron retentions were roughly proportional to the amounts ingested. The average iron balance for the subjects in Group I on milk alone was minus 0.005 mg./kg./day (−0.127 to +0.050). When they were fed milk and meat, the average balance was plus 0.248 mg./kg. (+0.129 to +0.460). In Group III the average retention of Fe on milk alone was minus 0.006 mg./kg./day (−0.053 to +0.025). When on meat alone the average retention was plus 0.237 mg./kg./day (+0.134 to +0.421). It is evident from this that the Fe in the meat is available for absorption in the intestine, and it is also apparent that the infants could change from a negative to a positive balance or the reverse within the foreperiod of each type of diet.

VI. ADDITIONAL CLINICAL OBSERVATIONS

Hemoglobin and total serum protein determinations were made at intervals on each infant, and the values are shown in charts 5, 6 and 7 with some figures from the litera-

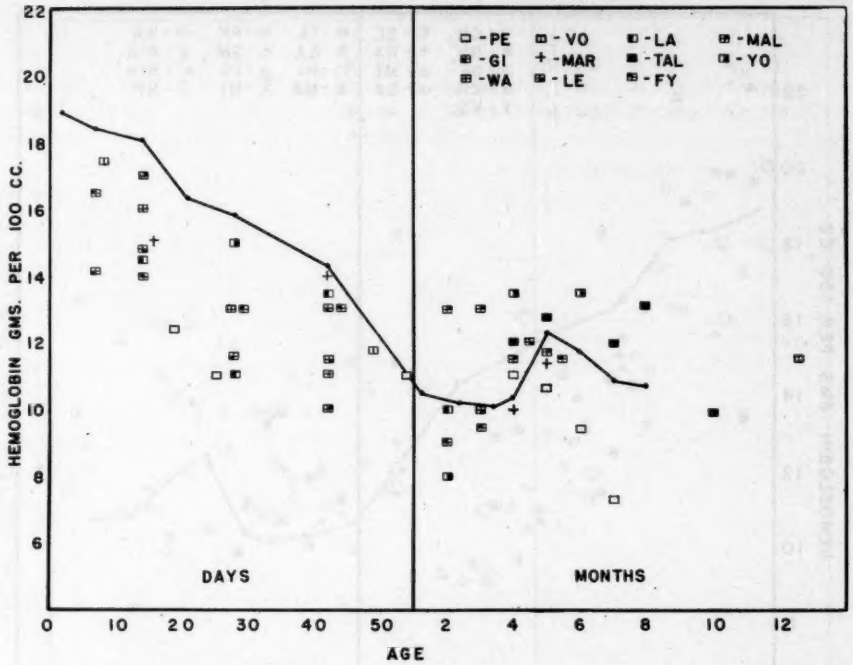

CHART 5. Blood hemoglobin values of 11 premature infants who received no meat at all during period that hemoglobin was followed. All but 2 infants received Fe as syrup of ferrous sulphate and transfusions where necessary as indicated below. Points connected by line are values for premature infants reported by Abt in 1935.[37]

Pe—No iron.
Yo—Transfusion. Iron 2 mo. plus.
Le—Iron 1-5 mo.
Fy—Transfusions. Iron 1-3 mo.
Tal—Iron 1 mo. plus.
Wa—Iron to 3 mo.
Mal—Iron 2-4 mo.
La—Iron 2 mo. plus.
Gl—Iron 1-2 mo.
Mar—Iron 1-2 mo. and 5-6 mo.
VO—No iron.

ture for comparison. As many subjects as possible were followed in the outpatient department after discharge, while continuing on meat-supplemented formulae. The physiologic fall in hemoglobin and total protein was not stopped by the substitution of meat in the diets in the early weeks, or by its addition to the diet later on. A larger and more closely followed series would be necessary to determine the effect of continuous meat supplementation on the hemoglobin picture during the first year of life.

The average daily weight gains during the foreperiod and collection period of the subjects in Group I on the control formulae was 34.5 gm./day, and was 25.0 gm./day for this group on the meat-milk formulae (table 2). These figures would have been more nearly the same except for the poor gains of two of the infants on the test diets. The weight gains of the Group III subjects were the same on both control and meat formulae . . . 25.0 gm./day.

There was no significant difference in the average number of stools per day on the

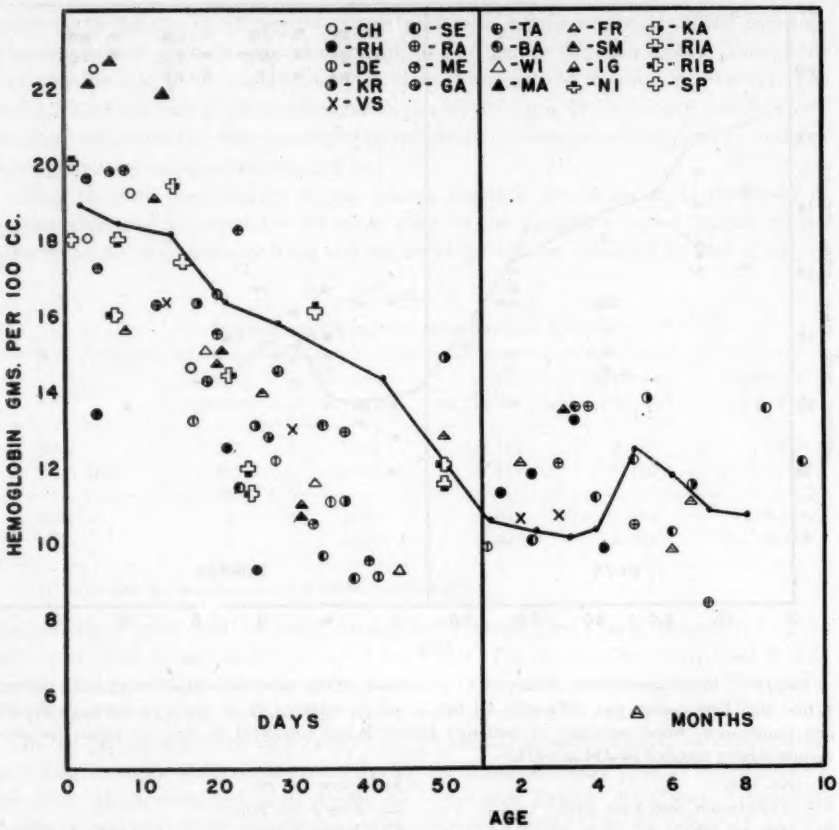

CHART 6. Blood hemoglobin values of 21 premature infants who received meat at some time during period hemoglobin was followed. Some infants in this group also received Fe and transfusions where necessary as indicated below. Where mothers failed to cooperate exact period of meat feeding is unknown. Points connected by line are values for premature infants reported by Abt.[37]

Ch—Meat 4-6 wk.
Rh—Meat 5-10 wk.
De—Meat 5-8 wk.
Kr—Meat 2-13 wk. Transfusion.
Se—Meat 1-9 mo. Transfusion and iron.
Ra—Meat 2-16 wk.
Ga—Meat 3-4 wk.
Ni—Meat 2 wk. plus.
Ta—Meat 2-4 wk.
Ba—Meat 1-4 wk.
Sp—Meat 3-4 wk.
Wi—Meat 6-7 wk.
Ma—Meat 1-4 wk.
Fr—Meat 6-11 wk. Iron 5 mo. plus.
Sm—Meat 2-4 wk.
Ig—Meat 2-6 wk. Transfusion.
Me—Meat 2-7 wk. Transfusion and iron.
Ka—Meat 2-4 wk.
RiA—Meat 6-8 wk.
RiB—Meat 6-8 wk.
VS—Meat 3 wk. plus. Iron at 8 mo.

three types of diet. The stools darkened in color following the addition of meat to the diet, and for the first day or two on meat diets were softer in consistency than before. There was no instance of diarrhea or gastrointestinal disturbance, nor did any sign of sensitivity to the meat develop.

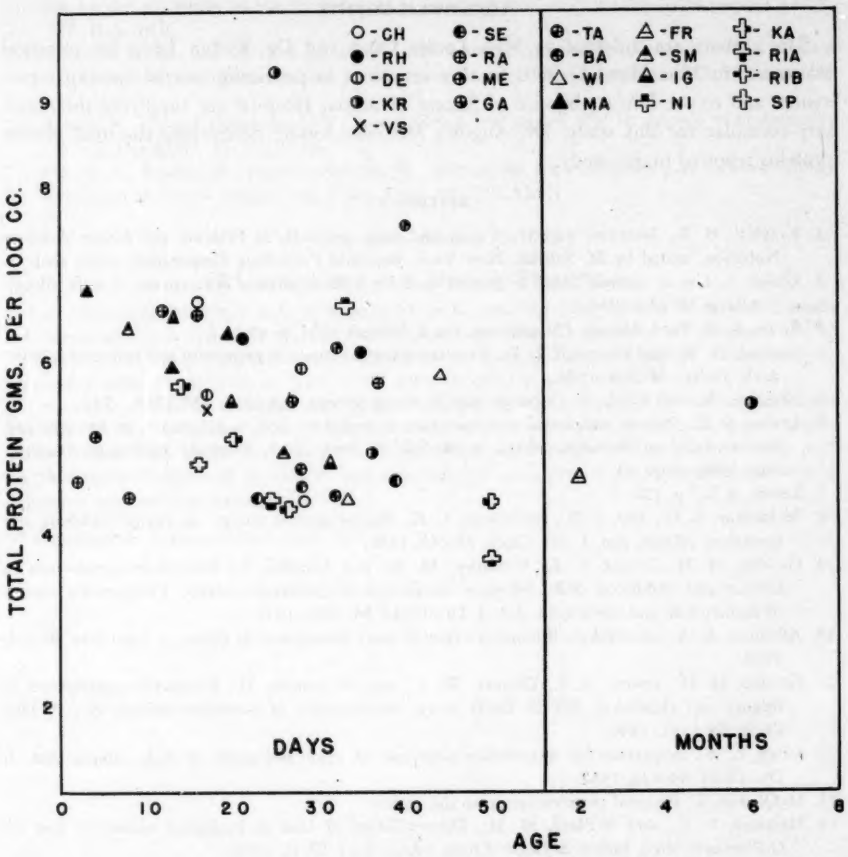

CHART 7. Blood plasma protein determinations on 21 premature infants who received some meat. For key see charts 5 and 6.

CONCLUSIONS

Meat protein is as well retained and utilized as milk protein by the premature infant and is therefore as safe and efficient a source of protein as milk. The fat absorption of the premature infant is not significantly altered when the milk fat in the diet is partly or wholly replaced by meat fat or meat fat and olive oil.

Strained meats do not contain a sufficient quantity of Ca and P to maintain an adequate intake of these minerals for the premature infant without further supplementation from other sources such as milk or pure mineral supplements.

Strained meats are an excellent and readily available source of Fe for premature infants. The Fe of meat is absorbed by them, but how well it is stored and utilized by them requires further investigation.

Acknowledgments

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SPANISH ABSTRACT

El Uso de Carne en la Dieta de Prematuros

Los prematuros retienen y utilizan la proteina de la carne tan bien como la de la leche, siendo por consiguiente una fuente de proteina tan eficiente como ésta. La absorcion de las grasas por el prematuro no se altera significativamente cuando en su dieta se substituye parcial o totalmente la grasa de la leche por la grasa de carne, o por grasa de carne y aceite de oliva.

Las carnes coladas no contienen una cantidad suficiente de Ca y P para mantener un suministro adecuado de estos minerales, si el prematuro no los recibe de otras fuentes como la leche o suplementos de minerales puros. Las carnes coladas constituye una excelente fuente de hierro (Fe) para los prematuros. El hierro de la carne es bien absorbido por ellos, pero el grado de almacenamiento y utilizacion requiere mas investigacion.

35 Chittenden Avenue, Crestwood, N.Y.

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

DURING this year this space will be used, as it was last year, to inform members of the plans which have been formulated by the Executive Board and the President to enlarge the usefulness of our organization. It is not possible nor is it desirable to describe in a single page any program for the coming year. Furthermore, such a program may have to be changed. Therefore, you are asked to turn to this page every issue, for an attempt will be made to keep you informed of those developments which your officers consider vital.

When you receive your Blue Book, you will note many changes. Dr. Clifford G. Grulee is no longer the Secretary-Treasurer but is now Executive Secretary. He will remain in that capacity until his retirement July 1st. Dr. Einor H. Christopherson is at the present time without portfolio but will, after July 1st, be Executive Secretary. He made a deep impression on those who met him in Chicago. He is not given to making quick pronouncements, and he will not talk until he is acquainted with our program. For the most part he listened and thought. Those of us who got to know him best felt that he was made for the job he is about to undertake.

You will note also that Mrs. Jewel Bundy is the new Business Manager. We could not have found anyone who knows the Academy business better. In addition, she is universally liked by every member. Dr. Grulee will act as Treasurer. Dr. William J. Orr, who is the new Program Chairman, was the first choice for this position of all those I consulted. It is also a fact that the Executive Board has been enthusiastically unanimous in making these appointments.

In addition to these changes in personnel, there are changes in committees. These are due to the reorganization plan which created new standing committees. They are also the result of suggestions made by the membership for new scientific committees. Not all of the suggestions were thought to be practical, but two new scientific committees were formed, one on Mentally and Physically Handicapped Children, and another on Accident Prevention in Children.

I want to call your attention particularly to the two new committees which were set up by the Reorganization Committee. The first one is the Advisory Committee on

Child Health. It is planned that this Committee will be entirely advisory to the President and to the Executive Board. The Chairman of this Committee is the immediate past president, who will serve for one year. Its membership is composed of the chairmen of those committees which are considered most important in our administrative work; the Publications Committee, the Legislative Committee, and the Budget Committee; and three other members who are picked at large for their previous background of help to the Academy.

The other committee to which I would call your attention is the Liaison Committee. It has been felt for some time that one of the important aspects of our Academy work is better liaison with other organizations working in the field of child health. In order to strengthen this, the duty of this Committee is to aid the President in the proper selection of liaison representatives to other organizations and to suggest organizations with which we should have liaison. In other words, their major function will be to integrate our work with the universal goal of better health for all children.

PAUL W. BEAVEN, M.D., *President*

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Dr. Alex C. Zarchy
286 East Rockaway Rd.
Hewlett, L.I., N.Y.

Dr. W. Price Killingsworth
541 Ninth Ave.
Port Arthur, Tex.

The following members of the Academy have died recently.

Dr. Samuel Ash
866 S. 13th St.
Newark, N.J.

Dr. Benjamin Bashinski
Doctors' Building
Macon, Ga.
(Died May 21, 1950)

Dr. Arthur H. Gray
521-23 Medical Arts Bldg.
Seattle
(Died Sept. 9, 1949)

Dr. Abraham B. Grossman, Emeritus Member
2871 Hampton Rd.
Cleveland
(Died 10 years ago, Evanston Office notified Oct. 5, 1950)

Dr. Samuel I. Lebeau
5817 Darlington Rd.
Pittsburgh
(Died Oct. 11, 1950)

Dr. W. Roger Moore
206-7 Kirkpatrick Bldg.
St. Joseph, Mo.
(Died during week of Aug. 13-19, 1950)

Dr. L. Howard Smith
1020 S.W. Taylor St.
Portland, Ore.
(Died Dec. 1949)

Dr. Lewis K. Sweet
Gallinger Municipal Hospital
19th & Mass. Ave., S.E.
Washington, D.C.
(Died Sept. 24, 1950)

Dr. Henry Washeim, Jr., Emeritus Member
2648 Edgewood Rd.
Utica, N.Y.
(Died, Oct. 21, 1948)

Round Table Discussion

IMMUNOLOGY IN THE PRACTICE OF PEDIATRICS

JOHN J. MILLER, JR., M.D., San Francisco, *Chairman;* CHARLES E. SMITH, M.D., Berkeley, Calif.; PAUL HATTERSLEY, M.D., San Francisco; HENRY B. BRUYN, M.D., San Francisco

ROSEMARIE J. TURSKY, M.D., Harrisburg, Pa., and GILBERT J. LEVY, M.D., Memphis, Tenn., *Secretaries*

1. CLINICAL SIGNIFICANCE OF Rh SENSITIZATION

Dr. Paul Hattersley: I shall begin with an obvious oversimplification. I shall speak of *the* Rh factor. We all are aware that there are many Rh factors. However, it has been established that at least 99% of sensitizations within the Rh group of antigens are by the Rh_0 or D antigen. It is therefore almost entirely among individuals negative for this factor that sensitization occurs. On this basis it is clinically correct to classify individuals as Rh-positive or Rh-negative according to the presence or absence of this one important factor.

The Rh factor is a hereditary characteristic, inherited as a simple Mendelian dominant. Being antigenic, it is capable of stimulating the formation of antibodies upon reaching the body of an Rh-negative individual. There are 2 ways in which Rh-positive cells, containing the Rh antigen, can reach the circulation of an Rh-negative person. The first and most obvious is by intravenous or intramuscular transfusion. The second is by pregnancy. Small amounts of the blood of the fetus cross the placental barrier into the circulation of the mother. If the fetus is Rh-positive, and the mother is Rh-negative, sensitization of the mother to the Rh factor may occur.

There are 3 variable factors which, in different degree, determine whether an Rh-negative individual will become sensitized to the Rh factor. They are the total dose of Rh antigen received, the duration of time in which this dose is received, and the individual's antibody producing capacity. It is not surprising, therefore, that while the over-all percentage of sensitization by pregnancy alone is around 4%, the incidence of sensitization by transfusion approaches 50%. Actually, a single transfusion frequently produces a high degree of sensitization. To avoid this dangerous complication it is essential that all Rh-negative individuals be transfused with only Rh-negative blood.

More commonly recognized are the other undesirable results of Rh sensitization. When an Rh-negative woman who has been sensitized to the Rh factor, either by previous pregnancies or by transfusions, carries an Rh-positive fetus, her Rh antibodies pass across the placental barrier into the fetus, destroying his erythrocytes, and injuring other tissues. The result is hemolytic disease of the fetus and newborn infant, varying in severity from only the mildest of anemias, through severe jaundice to the stillborn hydrops.

The technics of prediction of hemolytic disease in the unborn infant, the methods of diagnosis once the infant is born, and available therapeutic measures are the most important matters for discussion today. There is a difference of opinion in regard to the tests which should be performed during the pregnancy of the Rh-negative woman whose husband is Rh-positive. Primrose and his group, on the basis of oft repeated antibody titrations, have classified the curves of antibody titers into 6 major groups. In group one the antibody first appears very late in pregnancy and the titer at term is still very low. The prognosis in this group is excellent. In the other groups, antibodies appear earlier, and rise to higher levels, with correspondingly more severe involvement of the fetus. These workers feel that a fairly accurate prognosis as to the outcome of pregnancy is possible by fitting a patient's titer curve into one or another of these groups. Page emphasizes the importance of the time at which antibodies first appear, feeling that the titer or type of antibodies is of less

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importance. If antibodies first appear less than 10 weeks before term, the outlook for the baby is good. If they first appear between 10 and 16 weeks before term, the outlook is less favorable, but may be improved by early delivery. On the other hand, if antibodies appear more than 16 weeks before term, the outlook is so poor that early delivery is not warranted. Davidson feels that the type of antibody is more important than the titer or the time of its appearance. The least dangerous is the saline agglutinin, while the albumin agglutinin (cryptagglutinoid) and true blocking antibody are progressively more dangerous.

Such statistical approaches to prognosis are valuable as guides, but are not too reliable in the individual case because of the relatively frequent exceptions. In general, the earlier an antibody appears, and the higher its titer, the worse is the prognosis. If antibodies of the blocking type appear, the prognosis may be considered particularly grave.

It is the practice at Stanford to do periodic Rh antibody tests on all pregnant women who are Rh-negative and who have Rh-positive husbands. If antibody is encountered, the period between tests is decreased. In the final analysis, however, it appears that the patient's history is of great prognostic value. If there have been previous erythroblastotic infants, the outlook is not good, and if there have been transfusions of Rh-positive blood, the prognosis is particularly grave.

When one is presented with an infant from a sensitized Rh-negative mother, there are a number of diagnostic steps which must frequently be taken to determine whether the child has hemolytic disease. Of course the diagnosis may be obvious, with marked pallor, jaundice, splenomegaly and edema. Suffice to say that all these signs may occur in diseases other than hemolytic disease but any one of them is suggestive, and the combination of several makes the diagnosis fairly clear. In many cases, however, the infant at birth appears entirely normal and laboratory analysis is essential for diagnosis.

The laboratory signs of hemolytic disease are: (1) Anemia. A hemoglobin of less than 14 gm.% in the newborn infant is usually a sign of impending trouble. (2) Bilirubinemia. A cord serum bilirubin of more than 4 mg.% may be considered a sign of hemolytic disease. (3) Erythroblastosis. As many as 1000 nucleated red cells/cmm. may occur in a variety of neonatal conditions, but numbers above that level require definite explanations. On the other hand, not every child with hemolytic disease has an elevated erythroblast count, while very high figures may occasionally occur in infants born to diabetic mothers. (4) Incompatibility between cells of infant and serum of mother. Since the vast majority of cases of hemolytic disease are due to Rh_o sensitization of the mother, she will in most cases prove to be Rh-negative, with Rh antibodies in her serum, and her affected infant is Rh-positive. Occasionally sensitization to some other blood factor is responsible for hemolytic disease, and such an incompatibility can be demonstrated. Without a demonstrable incompatibility, the diagnosis of hemolytic disease due to maternal sensitization should not be made. (5) Sensitization of the infant's erythrocytes. If Rh antibodies have reached the circulation of the infant in sufficient quantities to cause disease, they are adsorbed on the surface of the infant's erythrocytes. Such adsorbed antibodies may be demonstrated by the Coombs test, utilizing the antihuman globulin precipitin, or by a simpler technic based on the agglutination of sensitized cells by serum, plasma, albumen or some other colloidal substance. I have yet to see a case of hemolytic disease due to Rh sensitization in which adsorbed antibodies could not be demonstrated by one or both of these methods.

There is as much difference of opinion regarding the correct methods of treatment of hemolytic disease as there is regarding prognosis. A very considerable percentage of cases can be treated quite adequately by simple transfusions, as indicated by the falling hemoglobin. In those cases where there is no ominous history of maternal transfusions or of siblings with disease, where the titer appeared late and did not reach a very high level, and where there is little clinical or laboratory evidence of disease at birth, this is probably the correct means of treatment.

There are cases, however, and they are not rare, which cannot be saved by simple transfusion. Even though the hemoglobin may be brought up to perfectly normal levels, and maintained there, some infants will develop progressive evidence of hepatic and central nervous system disease, and succumb. Unfortunately it is not easy to predict which cases will follow this course.

It seems obvious that a large part of the damage in such cases is being incurred after delivery. It is not difficult to assume that the damage is in some way associated with Rh antibodies which remain in the baby's blood, or perhaps with the breakdown products of the infant's erythrocytes. If such be the case, it seems desirable to remove the baby's blood, hoping to remove the noxious agent and arrest injury to the tissues.

Various technics for exsanguination transfusion have been perfected. At Stanford we have used a variation of Diamond's method, using a plastic catheter which is inserted into the umbilical vein. When blood can be withdrawn freely the procedure is started, alternately withdrawing 10 to 20 cc. of blood from the infant, and replacing it with freshly drawn citrated blood. We usually use approximately 500 cc. It is usually wise to complete the procedure by injecting 50 cc. more than has been withdrawn. The procedure is not a difficult one. As it should be performed when the infant is only a few hours old, prompt diagnosis is essential. The improvement in the affected infant is usually remarkable, and we have encountered no sequelae which could be ascribed to the procedure. Further transfusions have rarely been necessary, and the child usually goes home with his mother. Our experience is in agreement with that of Diamond, that this is a valuable technic, and at times may be life saving.

Perhaps the most violent differences of opinion in this field can be precipitated by a discussion of the pros and cons of early delivery. This is probably due to the fact that it is impossible to prove whether early delivery has ever saved a life or not. A baby delivered early is subjected to the dangers of prematurity. A week or two usually constitutes no serious danger, but prematurity of a month or more is a factor to reckon with. However, it is not unusual to see an infant who, in the face of an ominous history and a rising antibody titer, was delivered early and who, although severely affected, made a satisfactory recovery following exsanguination transfusion. With proper care few of these infants die. In some cases it is almost inconceivable that pregnancy could have gone to term with anything but a stillborn hydrops resulting. It is my very definite feeling that in certain selected cases early delivery, whether by induction or cesarian, is indicated.

Dr. Albert M. Jones, Memphis, Tenn.: You report one thousand nucleated red cells/cmm. as being abnormal. I would like you to make a few remarks about the habit of laboratories of recording the number of nucleated red cells as so many per 100 wbc's. When you consider that the white cells vary so much, with 20,000 in one baby, and 10,000 in another, isn't it difficult to get any clear understanding of the picture when the nucleated red cells are reported in this way?

Dr. Hattersley: Your point is well taken. Nucleated red cells should be expressed in terms of number per cubic mm., rather than per 100 wbc's. On the other hand, if it is reported in the latter way, and there is a white count reported, you can easily convert to absolute figures.

Dr. Alfred D. Biggs, Chicago: I belong to a group in Chicago which has definitely come to the conclusion that it is dangerous to take the bably early, even though the titer may go up later. Bitter experience has borne out the fact that they are better off if we leave them alone.

Dr. Thomas Perry, Los Angeles: I wonder if Dr. Hattersley would like to comment on a statement that Dr. Diamond made this morning. He stated that in Boston they had better results with replacement transfusion treatment of erythroblastosis fetalis when they used Rh-negative blood from female donors as compared with male donors. What is the immunologic basis for this?

Dr. Hattersley: I hadn't heard that before and have no idea how to explain it.

Dr. C. Hall Farmer, Macon, Ga.: I wonder whether we should use the replacement transfusion, or even small transfusions, since they may keep alive infants with cerebral damage. I have had the misfortune of observing two such babies in the past year. One of them had a very definite severe erythroblastosis which was treated with a replacement transfusion. This child is now perfectly well. The other child showed very mild jaundice and moderate anemia, and was brought into the hospital at 18 days. There was no question about the Rh incompatibility. We treated him with small repeated transfusions. He now has very definite evidence of kernicterus, and is not developing as he should.

Dr. Hattersley: It isn't always the most anemic or most jaundiced infant who will develop evidence of central nervous system damage. Sometimes, as in your second case, there was little of the usual evidence of disease, but central nervous system damage did occur. This is not infrequent. However, I do not feel that the rather low incidence of permanent defects in these children is a contraindication to proper transfusion therapy in an effort to save their lives.

2. DIAGNOSTIC IMMUNOLOGY IN VIRAL AND RICKETTSIAL DISEASES

Dr. Henry B. Bruyn: While the most important diagnostic criterion in viral disease is the isolation of the causative agent, the procedures necessary to accomplish this are so complex that this criterion is not often available to the practicing physician. The development of technics for the detection of alterations in the immunologic status of the patient with viral disease offers more practical and more

readily available means of diagnosis. The development of stable, noninfectious diagnostic antigens gives promise that in the future laboratories throughout the country will undertake viral and rickettsial serologic tests which are now performed for the most part only in specially equipped laboratories. The diagnostic immunology of some virus diseases of pediatric importance will be discussed in brief.

Influenza

Serologic means of establishing the diagnosis of influenza have been available for the past 15 years. As with most other virus diseases it is very important to compare 2 serum specimens—one taken early in the course of the disease, and the other taken approximately 10 days to 2 weeks later. This is especially true in the case of influenza since most adults possess circulating antibody to many of the strains of influenza.

There are 3 methods employed. The first, and the oldest, is the mouse neutralization test, in which the concentration of antibodies capable of neutralizing the virus is measured. While cumbersome and costly, it is used as a basis for evaluation of other serologic technics. The second test depends on the ability of influenza virus to agglutinate certain types of red blood cells, notably those of humans and of chickens. The degree of inhibition of this agglutination provided by immune serum parallels the protection given the mouse in the neutralization test. This agglutination inhibition test is relatively simple. It requires only chicken red blood cells and the virus. The third test employed is the complement fixation. This has the advantage of being less strain specific than the agglutination inhibition test. It is of value when the current epidemic strain may not be readily available.

Before leaving the subject of influenza, I might mention that infants seem to be as capable of producing antibody as older children and adults.

Epidemic Parotitis

Mumps has recently received a great deal of attention through the demonstration by serologic means of some of the ways in which infection with this virus may present itself. Mumps meningoencephalitis without parotitis, for example, has become a better known entity due to the use of serologic technics. The first to be developed was that of complement fixation. The antigen used is either infected allantoic fluid or other chick embryo tissues. The second method for detecting antibodies against mumps depends upon the ability of the virus, like that of influenza, to agglutinate chicken red blood cells. The inhibition of this agglutination by convalescent sera may be quantitated and compared to that of an earlier serum specimen. The antibody detectable by either of the above means may appear very early in the disease. The demonstration of a high titer in a single convalescent specimen is probably of great diagnostic significance.

Another immunologic technic of promise in the diagnosis of mumps is the intradermal test of Enders, employing killed virus. Skin reactivity has been correlated with clinical immunity. The value of this test in pediatrics should be great. It is conceivable that with the use of this test as a routine procedure at regular intervals in the course of a child's school years, the development of an immunity to mumps, following inapparent infection, could be detected.

Herpes

The virus of Herpes simplex is one of the commonest infectious agents in humans, causing diseases of the skin, mucous membrane, eye and the central nervous system. The commonest example of primary infection with the virus, occurring predominantly in the pediatric age group, is acute herpetic gingivostomatitis. While this disease rarely causes difficulty in clinical diagnosis, some of the other manifestations of herpetic infection, such as vulvovaginitis and meningoencephalitis, are less clinically specific and diagnosis depends upon the detection of an immunologic response to this virus.

The 2 serologic technics used in the detection of antibody to herpes simplex are the neutralization test, using embryonated chicken eggs or mice, and the complement fixation test. The latter is at the moment not used enough to warrant discussion at this time. Neutralization tests have been very useful in demonstrating the herpetic origin of some of the more obscure syndromes caused by virus. In the egg, the acute and convalescent serum specimens are compared on the basis of their ability to prevent the development of typical herpetic lesions on the chorioallantoic membrane of chicken embryos. In the mouse the protection afforded by the 2 serum specimens against a known strain of herpes virus is compared.

In recent years an intradermal test using killed herpes virus has been given a trial. As in the

case of the mumps virus intradermal test, a negative reaction to the antigen was related to the absence of neutralizing antibody, indicating no previous infection with this virus. From the practical standpoint an intradermal test might be of value in establishing, during convalescence, a diagnosis of primary herpetic infection.

Primary Atypical Pneumonia

This disease has become of increasing importance in the last year due to the demonstration of the therapeutic value of aureomycin. It is important for the pediatrician to become familiar with the variable manifestations of this infection in children. Serologic technics have shown that there may be upper respiratory infection without pneumonia.

The diagnostic procedures most commonly employed depend upon the appearance during the course of the disease of the so-called cold isohemagglutinins and the agglutinins for the streptococcus MG. Experience with the cold agglutinin test indicates that about 50 to 60% of all patients with primary atypical pneumonia will develop a significant titer, that is in excess of 1 to 40. Also, the more severe the disease, the more likely will cold agglutinins appear. The test is performed by mixing serial dilutions of the serum with a suspension of human Group O red blood cells and incubating the mixture at 4° for varying lengths of time. It is important to stress that specimens of blood for the cold agglutinin test should not be allowed to be chilled for the cold agglutinin will be absorbed on the homologous cells and thus discarded with the clot.

Cold agglutinins are also found in the sera of cases of sickle cell anemia.

Mention should also be made of another virus producing the picture of nonbacterial pneumonia, that is psittacosis. The serologic technic most commonly used for identification is complement fixation.

Infectious Mononucleosis

While the etiology of this disease is yet unproved, it is customary to assume a virus agent. Besides the typical clinical and hematologic diagnostic criteria, the serologic demonstration of agglutinins in the patient's serum against sheep red blood cells is of great diagnostic significance. These so-called "heterophile antibodies" may appear at any time from the fourth day of disease onward, but usually are present between the seventh and tenth days. The sheep cell agglutinin of infectious mononucleosis, in contrast to that which may appear following injections of horse serum, is not absorbed on guinea pig kidney. The disagreement concerning the diagnostic titer of heterophile antibody in infectious mononucleosis is explained by variations in technics in different laboratories. In general titers of from 1 to 10 to 1 to 40 should be considered negative, titers of from 1 to 80 to 1 to 160 suspicious, and titers of 1 to 160 or more positive.

Virus Infections of the Central Nervous System

The clinical differentiation between the various encephalitides is almost impossible and serologic procedures present the only means of determining the etiology (other than isolation of the agent, usually at post mortem). The serologic tests used are the neutralization test in mice and a complement fixation test using specific virus antigens. The agents most commonly tested for are Western equine encephalitis, St. Louis encephalitis, Eastern equine encephalitis, mumps, and lymphocytic choriomeningitis. Practical laboratory tests for the diagnosis of anterior poliomyelitis are not yet available.

Rickettsial Diseases

The serologic diagnosis of epidemic typhus, murine typhus, scrub typhus, Q fever, Rocky Mountain spotted fever and rickettsial pox are most commonly made through the use of complement fixation tests using specific rickettsial antigens prepared from fertile hens' eggs. These antigens are stable and may be stored for indefinite lengths of time in an ordinary ice box. Agglutination tests using suspensions of living rickettsia are performed in some laboratories but due to the danger of infection the complement fixation test is preferable. The titer of complement-fixing antibodies in this group of diseases usually shows a rise by the 10th day of disease. Cross reactions are common. For example, in rickettsial pox, a disease of recent discovery important in the pediatric group, the complement-fixing antibody for Rocky Mountain spotted fever antigen is as high as is the complement-fixing antibody for the rickettsial pox antigen.

The Weil-Felix reaction has been a very useful and simple procedure which can be performed

accurately in almost any hospital laboratory. This test depends on the development of agglutinins against the OX-19 and OX-2 strains of bacillus proteus during the course of epidemic or murine typhus and Rocky Mountain spotted fever. In Q fever no agglutinins develop against the proteus strains. A difficulty in the test lies in the fact that the agglutinin titer may rise under other conditions than infection with these rickettsial agents. The distinct advantages of the test include the fact that agglutinin develops between the first and eighth day of the disease and this early appearance of antibody together with the relative simplicity of the test has made its use more widespread than the complement fixation test.

By way of summarizing the discussion, it may be said that serologic means of diagnosis of viral and rickettsial diseases are becoming more available and knowledge of the technics used should become a part of the diagnostic armamentarium of the practicing physician. Where diagnostic laboratory facilities are available, the practicing physician has demonstrated increasing interest in proving serologically the etiology of the virus diseases he is called upon to diagnose. The promise of more effective therapeutic agents for diseases of viral and rickettsial origin makes more important the early clinical diagnosis. Improvement in our diagnostic ability will come with the use of serologic tests correlated with the clinical findings.

Discussion

Dr. M. I. Vinnecour, Beverly Hills, Calif.: I would like to know at what times one should obtain the 2 blood specimens for serologic tests.

Dr. Bruyn: The earlier the better for the "acute" blood and, in most virus diseases, between 10 and 14 days after the onset for the "convalescent" blood.

Dr. Vinnecour: In regard to storage, does the blood have to be frozen?

Dr. Bruyn: No. If the serum is separated from the clot under sterile conditions, it can be stored for some length of time in any ice box.

Dr. Joseph A. Schaefer, Portland, Ore.: How soon after the onset of mumps does the skin test become positive?

Dr. Bruyn: The investigations on that have been carried out by Dr. Enders in the greatest detail and there is apparently a variable length of time, usually several weeks.

Dr. Howard Hildebrand, Ames, Iowa: Does the mumps virus skin test result in antibody production?

Dr. Bruyn: Yes, it produces antibody titers as measured by agglutination-inhibition and by complement-fixation.

Dr. David M. Goldstein, Beverly Hills, Calif.: Does aureomycin or chloromycetin affect the production of cold agglutinins in primary atypical pneumonia?

Dr. Bruyn: Chloromycetin has received very little investigation in primary atypical pneumonia, but in the group studies at Fort Ord by Meiklejohn and Shragg there was a significant difference between the number of positive cold agglutinin titers in the aureomycin treated group, as compared with the control group which was treated with penicillin. In other words, the controls untreated had a greater percentage of significant rises in titer. I am told, however, that experience elsewhere in the country has not been as clearcut as this.

Dr. Goldstein: Should that deter one from making the diagnosis and giving aureomycin?

Dr. Bruyn: No.

Dr. D. W. Van Gelder, Baton Rouge, La.: What has been your experience as to the duration of the titer following influenza vaccination in children?

Dr. Bruyn: We have tested a few children approximately 9 months following vaccination and have found the antibody titer at that time to be higher than it was before vaccination.

Dr. Biggs: I wanted to ask if the viruses of influenza are separate and apart from the viruses that cause the common cold?

Dr. Bruyn: They are quite separate, and a virus causing a syndrome like the common cold has recently been isolated both in England and in America and transmitted to volunteers.

Dr. Jones: From your experience do you think we should advise routine influenza immunization?

Dr. Bruyn: That is a very tough question. In the last year, as you know, the type A influenza strain that appeared was antigenically different from those strains present in the previously available commercial vaccines. It was found that even upon incorporation of the current or epidemic strain in the vaccine that the protection afforded the patient was not good. I think a good deal more experience

is going to be needed in the experimental use of univalent vaccines containing the various strains of influenza before one can explain that. However, there seems to be less variability in strains of influenza type B. An epidemic of influenza type B may appear and the protection afforded a patient against influenza type B has been shown to be good. Therefore, I think that as it applies to type B there would be some value to immunization. I think it would be better to wait until it was apparent that an epidemic was in progress before advising routine immunization.

Dr. Thomas Chalkey, Richmond, Va.: How about the use of immune gamma globulin in infectious mononucleosis?

Dr. Bruyn: It has been claimed to be of value. However, when large amounts of gamma globulin were given to alternate cases in a group with which I am familiar, no apparent therapeutic effect was evident.

Dr. Goldstein: Have you had any experience in specific treatment against the polio virus?

Dr. Bruyn: No. As you may know, in the Children's Hospital in San Francisco, Dr. Shaw uses pooled plasma almost routinely. There has been a paper recently, which suggests a possible explanation of the fortunate clinical results which are occasionally noted. It was asserted that the beneficial effects resulted from a diminution of edema in the spinal cord by means of increasing the oncotic pressure of the blood. Since all the clinical signs of polio are not due to infected nerve cells but also to the temporary damage from the pressure of edema, the plasma is claimed to remove this edema, and to relieve the pressure on otherwise functional motor nerve cells. I think it is still in the realm of philosophy. The use of gamma globulin in large amounts in acute poliomyelitis has been investigated under very carefully controlled conditions and has been found of no value.

Dr. Van Gelder: How long does a heterophile antibody titer remain above 1 to 160 in infectious mononucleosis?

Dr. Bruyn: Some patients have been shown to lose their high titer very rapidly. Others may maintain high titers for as long as 2 or 3 months from the date of onset without clinical disease being apparent. However, the fact that there are cases of infectious mononucleosis that have lasted clinically as long as 2 or 3 months would lead one to believe that perhaps the persistence of the titer is the result of the disease being present.

Dr. Hattersley: Do you feel that a diagnosis of infectious mononucleosis can be made with a titer which is below the diagnostic range following the absorption on guinea pig kidney, demonstrating that the heterophile antibody, though not of a high titer, is of the infectious mononucleosis type?

Dr. Bruyn: We have had several cases where we have been forced to that conclusion. I am not acquainted with the opinion of others on that point, but there has been doubt raised as to the absolute specificity of the guinea pig kidney absorption phenomena.

Dr. Vinnecour: It was interesting to hear the paper on tularemia given this morning. There were many cases where the heterophile antibody titer was up to 1:240.

Dr. Bruyn: Yes, I heard about the paper. There are various other diseases in which it is found to go up, but I believe those titers can often be absorbed out on guinea pig kidney. That has been shown to occur in people who have been sensitized in the past to horse serum, perhaps having received tetanus antitoxin. There is an anamnestic response of the heterophile antibody. There has been work done showing that there is a rise in antibodies against brucella and typhoid, for example, during the course of infectious mononucleosis.

Dr. Farmer: Would you comment on the value of cold agglutinins in viral infections other than primary atypical pneumonia?

Dr. Bruyn: The value of the cold agglutinin test in upper respiratory infections in childhood is perhaps academic. However, from our experience when it is done routinely, there will be a number of clinical entities showing a rise in cold agglutinin titer. We have been rather surprised at some of the syndromes that were associated with a rise. We also had the opportunity of working with the virus isolated from primary atypical pneumonia by Dr. Monroe Eaton, using that virus in a neutralization test. Eaton showed that a syndrome not unlike the common cold was associated, not only with a rise in cold agglutinins, but also with rising neutralizing antibodies against this virus.

Dr. Thomas Myers, Huntington Park, Calif.: Is there anything new with regard to laboratory aids in diagnosing either recent or latent undulant fever?

Dr. Bruyn: The only new work with which I am acquainted is the use of the blocking antibody technic which is still in the experimental stages. The use of complement-fixation tests, opsonocytophagic index, and the agglutinin titers remain the 3 serologic technics at the moment.

3. IMMUNOLOGY OF MYCOTIC INFECTIONS

Dr. Charles E. Smith: Because our experience has been greatest in the field of coccidioidomycosis and diagnostic procedures are further developed for this infection, our remarks will focus on it. The use of the coccidioidin skin test is generally accepted as the first step in establishing the diagnosis of coccidioidal disease. The intradermal coccidioidin test with a 1:100 dilution has the same relative significance as has the Mantoux tuberculin test. Unless there is a "conversion," a positive test cannot establish the time when an infection was acquired, as sensitivity is of many years' duration. However, unless the time is early in the course of a primary, nondisseminating infection, a negative test eliminates the diagnosis of primary infection. Since coccidioidal erythema nodosum occurs only when sensitivity is maximal, failure to react to coccidioidin eliminates a coccidioidal etiology of erythema nodosum. Because of discomfort to the extremely sensitive, it is advisable first to try 1:1000 or even 1:10,000 coccidioidin if one suspects that erythema nodosum is coccidioidal. In other cases in which nondisseminating primary coccidioidal infection is suspected, the possibility should be kept in mind that the patient who fails to react may not have developed sensitivity. Within the first week of onset approximately one-sixth are still negative. However, unless dissemination occurs, all react after the third week.

If dissemination (coccidioidal granuloma) threatens or has occurred, anergy is frequent. There is evidence that the coccidioidin test itself has prognostic significance. Among these patients with extrapulmonary lesions, 75% who continue to react to 1:100 coccidioidin recover, while only 17% of those who fail to react survive. When the patients fail to react even to 1:10 coccidioidin, only 10% survive. Although not invariably the case, frequently individuals who are recovering from disseminated disease establish or re-establish dermal sensitivity.

Coccidioidin is relatively stable if kept uncontaminated. If refrigerated it remains fully potent even in 1:100 dilution for over a year. It should be added that coccidioidin is now available commercially from the Cutter Laboratories, Berkeley, Calif.

Serologic tests are very useful in diagnosing active coccidioidal infection. First, however, coccidioidin should be used as a screen. Unless dissemination is suspected or, rarely in patients with thin-walled cavities suspected of being coccidioidal, serologic tests are wasted if the patients fail to react to coccidioidin. We have developed precipitin and quantitative complement fixation tests. They are specific except possibly for a few other deep mycotic infections. One or both tests are positive in over 99% of patients with disseminating disease, 93% of patients with primary nondisseminating illness, but only in 7% of persons with asymptomatic primary infections. Serology is negative or equivocal in two-fifths of the patients with pulmonary coccidioidal cavitation and usually is negative in patients with asymptomatic pulmonary residual lesions. The persistence of the diagnostic humoral antibodies is much less than is dermal sensitivity.

Among patients with primary nondisseminating coccidioidomycosis who at some time demonstrate positive serology, precipitins are present only in half the specimens during the first week. The proportion mounts progressively until the fourth week, when 84% are positive. The precipitins then decrease and after 3 or 4 months they are very infrequently present. Complement fixation develops more slowly but persists longer. It should be noted that in contradistinction to the two specimens necessary for serologic diagnosis in viral and rickettsial infections, a single positive specimen will establish the diagnosis of coccidioidal infecton.

While the precipitin tests appear to have only diagnostic significance, complement fixation tests also have prognostic connotations. Among more than 1700 patients with primary nondisseminating coccidioidal infections and whose sera fixed complement, approximately 98% had titers no higher than 1:16. Even fewer patients with coccidioidal cavities had this high a titer. On the other hand, 60% of over 400 patients with disseminating infections had titers greater than 1:16. Of those with extensive and fatal disseminations, 90% exceeded this level. As an individual recovers, the titer of the complement fixation regresses.

Skin tests and serologic tests for histoplasmosis and blastomycosis are available but their specificity and applicability are still under study. Histoplasmin is available for the Tuberculosis Control Division of the United States Public Health Service and from the Eli Lilly Company, Indianapolis, Ind. Blastomycin has been provided by Dr. Martin and Dr. Conant of Duke University School of Medicine. Serologic tests have been performed by the latter workers and by investigators at the Microbiological Institute of the National Institutes of Health, the Army Medical Center, the Tubercu-

losis Control Division of the Public Health Service, the Vanderbilt University School of Medicine and New York State Health Department.

Chairman Miller: Dr. Charles E. Smith is the authority on coccidioidomycosis. What he has told us is the result of many years of study. Are there any questions?

Question: Would you explain more about the specificity of coccidioidin and histoplasmin?

Dr. Smith: Apparently there are frequent cross-reactions between histoplasmin and blastomycin, both when they are used for skin tests and when they are used as antigens in serologic tests. Coccidioidin is much less likely to exhibit cross-reaction, but it occasionally does so. Certainly, if one is using it in concentrations greater than 1:100 the possibility of cross-reactions must be kept in mind.

Of aid in establishing these differentiations is the geographic distribution of the various mycoses. Coccidioidomycosis is endemic in the arid Southwest. Histoplasmosis and blastomycosis are virtually never acquired in that area. On the other hand, except under exotic circumstances, coccidioidomycosis is not acquired in the Mississippi Valley area where histoplasmin sensitivity is so frequently demonstrated.

Dr. C. E. Roach, New August, Ind.: Have you any evidence that repeated skin tests affect the sensitivity of the skin or the serologic tests?

Dr. Smith: Absolutely none. We have performed repeated skin tests without sensitizing men or animals. A soldier assigned to work with us at one of the San Joaquin Valley Army Air Fields took a test every time we came to his field. He was negative 12 times. At the time of his 13th test he was undergoing a coccidioidal infection and was positive. Coccidioidin does not have the disadvantage of brucellergin in interfering with subsequent serologic tests. Furthermore, it does not have the hazard of activating or exacerbating an infection. Occasionally, coccidioidin may evoke erythema nodosum in an individual undergoing a primary infection, but this does no real harm. Thus coccidioidin should not be withheld on the grounds for which we may withhold other types of skin tests.

Dr. E. A. Harrison, Birmingham, Ala.: I want to ask if there is any cross-reaction between histoplasmin and tuberculin. In 1945 I ran a series on patients routinely admitted to the hospital. The only histoplasmin reactors also were tuberculin reactors.

Dr. Smith: We are certain there is no cross-reaction between tuberculin and histoplasmin or coccidioidin. However, within this mycotic framework there certainly are cross-reactions which will have to be defined more accurately in future years.

Furthermore, one should beware of antigen adsorbed on syringes or diluting equipment. Autoclaving will not destroy the active principle. Syringes should be kept separate or boiled or soaked overnight in dichromate cleaning solution before re-use.

4. IMMUNIZATION PROCEDURES

Chairman Miller: In the application of immunology to the prevention of disease by active immunization, new questions and problems continue to arise. At the present time perhaps the most important question is in regard to the safety of H. pertussis vaccine. It is not entirely safe as recent reports have emphasized. But is it, or is it not, safe enough to employ routinely? I will briefly review the reports of tragedies occurring after its use.

In 1933 Madsen described 2 deaths in newborn infants occurring a few hours after second injections of saline suspended vaccine. In 1946 Werne and Garrow described 2 more instances in 10 month old twins occurring after second injections. Vomiting and somnolence were followed in a few hours by death. At autopsy "lesions referable to arterial spasm and to increased endothelial permeability" were found. They were attributed to delayed anaphylactic shock. A case of somnolence and flaccid paralysis following a fourth injection of vaccine, and terminated by death from pneumonia, was recorded in 1947 by Brady and Sorley.

In 1948 Byers and Moll reported 15 cases of encephalopathies following injections of H. pertussis vaccine during a period of 10 years. As symptoms in 6 instances appeared after the first injection anaphylaxis appeared unlikely. Furthermore when symptoms followed second and third injections, the incubation period was usually longer. This also was not typical of allergic reactions. It is my opinion that these cases of encephalopathy can be attributed most rationally to H. pertussis toxin which is known to be neurotropic in experimental animals.

By questionnaire, Toomey has collected 38 additional cases of convulsions occurring after H.

pertussis vaccine. At least 3 of them terminated fatally. Also Globus and Kohn very recently published a report of 2 more cases of encephalopathy. Both of these occurred after second injections. In one, which was fatal, a soluble H. pertussis filtrate had been employed.

The question, of course, is, whether these tragedies are sufficient in number to outweigh the routine use of H. pertussis vaccine? Although my answer is conditioned by my good fortune in not encountering any severe reactions (with the exception of one febrile convulsion in a child subject to febrile convulsions), I believe the value of H. pertussis vaccine outweighs the potential danger. Numerous field studies attest to the efficacy of vaccine in decreasing both the morbidity of and mortality from pertussis. In Sako's series alone, no deaths occurred among the vaccinated infants as compared to 15 deaths in his control group of similar size. Therefore, at least until a highly effective chemotherapeutic agent is found, and perhaps even if it is found, it seems to me that active immunization with vaccine is worth the risk.

How may the rare occurrence of crippling or fatal reactions be avoided? If toxicity of vaccine has been an important factor, the outlook is encouraging. The Division of Biologic Control of the National Institutes of Health has recently required that all vaccine be tested for toxicity before release. I do not know if any severe reactions have occurred with new lots of vaccine so tested. If so, they should be reported to that controlling agency. If, on the other hand, the majority of severe reactions, with or without involvement of the central nervous system, have been on an allergic basis, the outlook is not so bright. Allergic reactions to all type of vaccines, toxoids and serums have occurred and will continue to occur. They may be due to individual idiosyncracy to the preservatives employed or simply to the foreign protein present.

Systemic reactions I am sure can be minimized by adhering to the following dicta. Only well babies and well children should be inoculated. The presence of any illness, however minor, should be a contraindication to any prophylactic inoculation. An unusually long interval between injections rarely if ever interferes with the final development of immunity. Secondly, children with known cerebral damage should not receive H. pertussis vaccine or diphtheria toxoid. Children with histories of febrile convulsions should be inoculated first with a fractional dose. Likewise in asthmatic children fractional doses are advisable. However, in infants with eczema this does not appear to be necessary. When an infant is brought in for his second injection, it is of the greatest importance to question the parent in regard to any reaction to the first injection. Somnolence should be inquired about as well as fever. When these symptoms are described, the volume of the next injection should be decreased to 0.1 cc.

Febrile reactions in well children to full doses of vaccine can also be limited by the use of slowly absorbed vaccine and by the routine prescription of aspirin to be taken a few hours after the injection. Alum-precipitated or aluminum hydroxide adsorbed vaccine is more slowly absorbed than saline suspended vaccine and hence is preferable. The protein content in any one injection should be limited to a cell count of 20 billion.

Local reactions can be minimized by limiting the volume of the injection to 0.5 cc. and by giving it intramuscularly.

The second important question is at what age should immunizations be commenced. May I submit that we should strive to attain maximum protection against pertussis, diphtheria and tetanus with a minimum number of injections and do so as early in life as practicable.

In the last few years evidence has mounted that infants under 6 months of age can be protected against pertussis. I refer to the classical work of Sako and his colleagues in the U. S. Public Health Service. Their studies have been confirmed, mainly indirectly, by a number of workers. I believe the total evidence is ample to warrant commencing immunization against pertussis in the second month of life, that is between the 4th and the 8th week. Precipitated or adsorbed vaccine should be employed, not only because systemic reactions are less common but because it is more effective than saline suspended vaccine, at this tender age. The total dose should be at least 40 billion cells in my opinion. This dose is divided into 3 injections at intervals of not less than 4 weeks. This schedule of injections will probably protect 3 out of 4 infants against familial exposure for one year. If the injections are begun even earlier, that is during the first month of life, fewer individuals will be protected. If injections are delayed until 6 months of age, more individuals will be protected and certainly the duration of their immunity will be longer.

However, since pertussis in the first 6 months of life is a dreadful disease attended by serious

complications and a significant fatality rate, it seems clear that we should not wait until the 6th month of life simply to get higher and more durable protection. We can rely on a reinjection at 18 months of age to make our primary immunization more durable.

If we begin H. pertussis vaccine in the second month of life, can we give diphtheria and tetanus toxoid in combination with it? We wish to do so, because our objective is to minimize the number of injections. With respect to tetanus toxoid this question has been answered in the affirmative. Infants in the second month of life respond to injections of tetanus toxoid with the production of antitoxin. Apparently no immaturity of the antibody production apparatus can be invoked or detected when tetanus toxoid is injected. But can we employ diphtheria toxoid at this age? Can we protect against diphtheria in early infancy or do we need to do so? I will go over the evidence for and against this question.

The early evidence was unfavorable. However, it was obtained with old toxin-antitoxin and then with two doses of fluid toxoid. When Schick-negative infants (Schick-negative by virtue of transplacentally acquired antitoxin) were given 2 doses of fluid toxoid by Greengard, the majority of them became Schick-positive within 18 months. Furthermore, Cooke demonstrated that when combined adsorbed diphtheria and tetanus toxoid was administered to infants carrying passively acquired diphtheria antitoxin, the titer thereof was not augmented. In fact, the majority had less diphtheria antitoxin after their injections than before. At the same time these same infants were able to manufacture tetanus antitoxin.

Thus, there is substantial evidence that homologous passive antitoxic immunity may interfere with primary active antitoxic immunization. This would appear to negate our desire to add diphtheria immunization to pertussis and tetanus immunization during the early months of life. On the basis of this evidence the use of a triple mixture commencing in the second month of life would appear useless. However, when di Sant'Agnese gave 3 injections of adsorbed triple mixture beginning in the newborn period, diphtheria antitoxin in concentration of 0.03 unit/cc. or more was found in 77% of infants 10 months later. Seemingly his 3 injections of a triple mixture were potent enough to overcome the blocking effect of circulating antitoxin which Cooke could not overcome with 2 injections of double toxoids. Not only was di Sant'Agnese's total dose of toxoid larger but the contained pertussis vaccine may well have potentiated the antitoxic responses.

Since Ramon's early observations on the potentiating effect of bacterial suspensions on antitoxin production, there have been a number of field and laboratory studies on the comparative potency of toxoids with and without admixed bacteria. They have recently been reviewed by Fleming and by Edsall. For example, tetanus toxoid containing typhoid vaccine produces higher tetanus antitoxic immunity than does tetanus toxoid alone. And what concerns us particularly are the findings of Bell who showed that "children who received 2 doses of diphtheria toxoid mixed with H. pertussis vaccine before they were 6 months of age had fewer failures to immunize against diphtheria (8% Schick positive), than children receiving unmixed toxoid at any age (11% Schick positive)."

I believe this evidence of Bell and of di Sant'Agnese pointing to the superior diphtheria immunizing potency of toxoid mixed with H. pertussis vaccine warrants the trial of adsorbed triple mixtures under 6 months of age. In this way our goal of providing maximum early protection with a minimum of injections may be quickly attained.

A schedule for primary immunizations can therefore be outlined as follows.

1. At 4 to 8 weeks of age 0.5 cc. intramuscularly (right buttock) of alum precipitated, or aluminum hydroxide adsorbed, diphtheria and tetanus toxoids containing 15 billion H. pertussis (30 billion/cc.).
2. 4 weeks later (8-12 weeks of age) 0.5 cc. of the above (left buttock).
3. 12 weeks after second injection (20-24 weeks of age) 0.5 cc. of the above (left deltoid).
4. At 1 year of age Schick and Schick control (Toxoid 1-100). Smallpox vaccination.
5. At 18 months of age recall injection of 0.5 cc. of the above.

This schedule is similar to one devised by Dr. di Sant'Agnese. It differs only in commencing a month earlier and in prolonging the interval between the second and third injections to 3 months. This longer interval is advised to obtain higher final antitoxin titers as it has been shown that wide spacing of injections of adsorbed toxoids is superior to intervals of 1 month. The 30 billion H. pertussis contained in the first 2 injections of the mixture should be sufficient to obtain protection against pertussis during the interval between the second and third injections.

The effectiveness of this schedule might be expected to vary geographically. In communities where

the great majority of women of childbearing age are immune to diphtheria, potential interference by transplacentally acquired antitoxin might tend to reduce a little the effectiveness of the diphtheria component in the triple mixture. The more susceptible the population to diphtheria the more effective the schedule should be. From a public health point of view this is most desirable.

In private practice it is possible to combine a conservative attitude with some original observations on the degree of diphtheria immunity in one's own community. Whenever granted permission, I do Schick tests, suitably controlled, on mothers of infants 1 month old. When the mothers are Schick-positive (and to date about half of them have been) I proceed with the schedule just described. When the mothers are Schick-negative I follow a more conservative schedule of commencing with two injections of simple precipitated H. pertussis vaccine at monthly intervals. An injection of adsorbed triple mixture is then given at 5 months of age to complete the pertussis immunization. Two injections of adsorbed double toxoids at 7 and at 10 months of age then complete the basic immunizations with a total of 5 inoculations. It is interesting to see how readily mothers will consent to a Schick test when they are told that it may save their infant 2 injections.

In regard to recall ("booster") injections, the simplest procedure is to use a triple mixture about every 3 years. If one adheres to the schedule previously described in which the first recall injection is given at 18 months of age, the next one is then given at 4 years of age, or when the child enters kindergarten. Adsorbed diphtheria and tetanus toxoids containing H. pertussis vaccine in a volume of 0.25 cc. should be quite sufficient. Thereafter, similar or even smaller doses of the mixture may be given at 7 and 10 years of age. Recall injections of tetanus toxoid are the most important and in my opinion should be continued throughout life.

Before administering diphtheria toxoid, alone or in combination, at 10 years of age or older, it is certainly safer to test for diphtheria toxoid sensitivity with diluted fluid diphtheria toxoid. A 1-100 dilution is satisfactory. We routinely control our Schick tests with this dilution of toxoid. I believe that most of the marked local reactions which may result from recall injections of triple antigens are due to diphtheria toxoid sensitivity. Therefore, in the allergic child, it is wiser to pursue a more conservative course. Schick tests and diphtheria toxoid sensitivity tests are given at 3 year intervals. When these are read, the Schick test is almost always negative and the toxoid sensitivity test is often positive. In these circumstances, the triple mixture is not given. Pertussis vaccine and tetanus toxoid are mixed in a syringe and injected in a volume of 0.5 cc.

The immunization of Schick positive, toxoid sensitive individuals is of course difficult. In these children or adolescents one must first be sure that immunity is actually absent. The Schick test may be very difficult to read. A diphtheria antitoxin titration will often clear up the matter, for most highly sensitive reactors carry at least 0.01 unit or more of antitoxin per cc. In other words they are well protected. If, however, susceptibility is proved and marked toxoid sensitivity coexists, one must proceed cautiously with small doses of diluted fluid toxoid. The patient should return every second day for inspection of the reaction. The use of Bousfield's method, the sublingual administration of toxoid, should be useful under such circumstances.

In addition to routine recall inoculations, exposure is an indication for a specific recall injection. After exposure to pertussis an injection of 20 billion H. pertussis is advised. (This injection is of no value if the child has not received his primary course of immunization.)

When a previously immunized child is exposed to diphtheria, a number of factors must be taken into account. They are the immunization history, the record of past Schick tests, the likelihood of the existence of toxoid sensitivity and the intensity of the exposure. I like to do a Schick test controlled with toxoid diluted 1-100. The latter has a twofold value. It serves as a small but definite stimulus to antitoxin production and it serves as a guide to the safety of toxoid in case the Schick test becomes positive. In the latter event fluid, not precipitated, toxoid should be employed to obtain rapidly developing immunity.

When a previously immunized child is wounded, a "wound booster" of 1 cc. of fluid tetanus toxoid should be given regardless of whether the child was originally inoculated with fluid or with precipitated tetanus toxoid. Fluid tetanus toxoid is more reliable than precipitated tetanus toxoid as a rapidly acting secondary stimulus. Speed of response is essential in the wounded. Under certain unusual conditions, such as massive contamination, compound fractures and shock, sufficient speed of response may not be obtained even with fluid toxoid. Fatal cases of tetanus have been recorded in immunized soldiers after 2 to 6 days' incubation, despite a "wound booster" of fluid toxoid. Therefore, in such instances recourse should be had to the immediate protection conferred by tetanus

antitoxin (preferably 5000 units). We have been able to show that tetanus toxoid can be administered simultaneously in another extremity. The immediate rise in titer due to the injected antitoxin is followed by a secondary rise, an immune response to the toxoid, on the fourth to the sixth day. Thus, whereas simultaneous active-passive immunization is without value to an unimmunized wounded individual, it is practicable in a previously immunized individual. It results in immediate protection and at the same time obviates the use of repeated injections of antitoxin.

Dr. Myers: How serious are the ill effects of reinjection of diphtheria toxoid in a child because of sensitivity to the diphtheria toxoid itself?

Chairman Miller: There may be very severe inflammation, a general systemic reaction, convulsions or asthma. Fortunately severe reactions are rare.

Dr. Myers: In view of the fact that it is still considered advisable, at least by the laity, to give tetanus antitoxin when a child steps on a rusty nail, are we laying ourselves open to criticism or medical legal action in the event that we fail to give antitoxin?

Chairman Miller: Are you referring to a child who has been actively immunized?

Dr. Myers: Let's say that the period of immunity may have worn off.

Chairman Miller: It is quite safe to rely on the tetanus toxoid booster except after severe wounding, extensive lacerations, compound fractures, or shock. In these conditions I believe both toxoid and antitoxin should be administered for the reasons I have already mentioned.

Dr. N. Gildersleeve, Pasadena, Calif.: Is there ever any evidence that indicates that early immunization will influence the incidence of toxic or allergic reactions?

Chairman Miller: There is no evidence that I know of.

Dr. Vinnecour: I just want to add something about giving toxoid to adults. I was called upon to give it to a father who had a positive Schick test. I gave him 0.1 cc. diphtheria toxoid. He was ill with a temperature of 105°F. (40.5°C).

Dr. Perry: Do you believe it is desirable to deliberately avoid continuing pertussis immunization in all children after the age of 2 years in order that they may get pertussis?

Chairman Miller: No, I do not. I give boosters of pertussis vaccine at 3 year intervals until they are about 12 years of age.

Dr. Perry: Will these individuals get pertussis when they are 30 and are working?

Chairman Miller: Some of them may, of course. But then second attacks of pertussis are not uncommon, particularly in grandparents.

Dr. Percy Minden, North Hollywood, Calif.: Were toxic reactions to pertussis vaccine associated with any particular brand or type of product? Did any occur following the use of Sauer vaccine?

Chairman Miller: No, not with any particular brand. Some of Byers' cases may have occurred following Sauer vaccine for Dr. Byers stated that human blood had been used in the media on which some lots of vaccine were prepared. Byers' original article was published in PEDIATRICS (April, 1948).

Dr. W. F. Burdick, Washington, D.C.: May I comment on what I think is the cause of many of these troublesome local reactions? I should also like to suggest a technic which I have used for many years and found to be very satisfactory.

1. Withdraw the toxoid into the syringe. 2. Change to a clean needle if there is any material on the needle. 3. Holding the needle upward draw in .2 cc.–.3 cc. of air. 4. Point the needle downward so that the air rises to the top of the toxoid in the syringe. Immediately plunge the intramuscular needle to its depth at the site previously prepared for the injection with rubbing alcohol. 5. Pull on the plunger to be sure that blood does not rise in the syringe. 6. Force the material promptly into the muscle and follow with the .2 cc. = .3 cc. of air. 7. Withdraw the needle quickly and immediately press the area firmly with an alcohol sponge. This method prevents any of the material from getting into the subcutaneous tissues. It avoids (1) the troublesome hard areas which persists for a long time, (2) abscess formation due to the breaking down of fatty tissues irritated by the toxoid and (3) many local inflammatory reactions which never quite reach the stage of an abscess.

Dr. E. J. Denenholz, Modesto, Calif.: Do you have any feeling about the incorporation of parapertussis vaccine with pertussis vaccine?

Chairman Miller: I don't believe that it is necessary here. Although we found B. parapertussis in San Francisco several years ago, we have not isolated the organism recently. Its inclusion in a vaccine would have the disadvantages of diluting the H. pertussis and increasing the protein content.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THIS month's communication, from Dr. Allan M. Butler, is a comment on the effect of a capitation system of payment upon pediatricians. This question was first raised by Dr. Borden S. Veeder in the April 1950 issue of PEDIATRICS and was continued by letters from Mr. I. S. Falk and Dr. Veeder in the November issue.

DEAR DR. HARPER:

Dr. Veeder's interesting letter in the April issue of PEDIATRICS* is, indeed, as you comment, extremely provocative and deserving of considered discussion.

As I understand it, Dr. Veeder quite rightly emphasizes the importance of the pediatrician who practices as a family physician within an age limit. He is concerned with this pediatrician's future (in contradistinction to the pediatrician serving as a specialist or consultant) under a national medical program on an insurance or taxation basis. He feels that this pediatrician under capitation remuneration would be at a disadvantage as compared to the family practitioner without an age limit because the child who comprises 100% of the former's patients requires more care than the adult who comprises 66% of the latter's practice. Dr. Veeder, therefore, concludes that the family pediatrician could survive only under a fee-for-service method of payment.

Should this conclusion be correct, medical insurance whether voluntary or compulsory would indeed be handicapped as fee-for-service has proved so susceptible of abuse under a broad third party payment plan.† Hence it behooves us to enquire as to whether this conclusion is valid.

Shouldn't the capitation fee per patient per year be based on what fee results in an appropriate income for a designated category of care for an appropriate number of a

* PEDIATRICS 5:739, 1950.

† The Quality of Medical Care in a National Health Program, Am. J. Pub. Health 39:898, 1949.

specific category of patients? If so, the capitation fee per patient would vary with the service demanded per patient per year. According to the experience of the Health Insurance Plan, New York City physician services per year average approximately 13 from birth to 1 year, 4.0 from 1 to 19 and 4.7 from 19 to 70 or over. Thus if ten per cent of a pediatrician's patients are infants under 1 year his services would average 4.9 per year as compared to 4.8 for the practitioner whose practice is one-third children and two-thirds adults. If the medical services under the insurance scheme are provided by groups of physicians, as under H. I. P. and as recommended by many, remuneration for this difference in service could be covered by adjustment agreed upon by the group. Otherwise, it could easily be handled by a higher capitation for infants from birth to 1 or 2 years. Such adjustments would be simple administrative and paper work matters as compared to the administrative headaches and multiplicity of records under fee-for-service. The single notification of acceptance of patients with age designated would meet the requirements of physician remuneration until cessation of the family-physician relationship, when a discontinuance notice would be necessary. That the same sliding scale capitation fee would apply to pediatrician or internist caring for children appears correct. The public's preference for the trained pediatrician should be his competitive advantage. He should receive a special fee only when serving as a consultant, which he could do, if so qualified, in addition to his family physician capitation practice. For such consultant service he could be paid by fee-for-service or, if this was a considerable part of his practice, by part-time salary.

It would appear that the considered application of capitation should defend the interests of the family pediatrician and internist under a National Health program far better than would remuneration by fee-for-service. The latter demands excessive administrative red tape and paper work; it unduly subjects the efficient, conscientious physician's income to the drain of fees paid the inefficient and less scrupulous physicians; and it introduces a monetary consideration that tempts some physicians to do what a consultant or specialist could do better and so limits the quality of medical care. Moreover, in spite of such disadvantages it does not provide better protection of appropriate physician income or lessen public control of physician income under a broad prepayment plan. For under such a plan, voluntary or governmental, the public will have an important voice. This is inevitable as prepayment plans expand enough to satisfy the public's needs.

Dr. Veeder's comments and such as are recorded here indicate that the profession should be concerned not only about methods of payment but also about appropriate scales of remuneration under any third party schemes, past, present or future. We all hope prepayment, insurance or tax supported medical care will expand by evolution. Without forethought by physicians evolution from schemes for low income groups with low scale of physician remuneration may result in a lowering of physician income proportional to the decline in private non-insurance fee-for-service practice. Let's hope, therefore, that many will follow Dr. Veeder's example and make use of the opportunity offered by your column to contribute freely to a tolerant discussion of alternative solutions to the serious problems that confront our profession. The respected democratic process of debate should contribute to constructive action and protect physician income far better than the current Whitaker and Baxter "education campaign."

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TRENDS

By JOHN P. HUBBARD, M.D.,
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This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

AT THE present writing, the 81st Congress has reconvened but it is doubtful whether much, if any, attention will be given to the many health bills which have been discussed at such length in Committee and on the Floor. By the time this review and preview is published, the 81st Congress will have finally adjourned and all unfinished business in the nature of bills which have not been enacted into law will be washed off the slate. But this does not mean that the unresolved issues will necessarily be dead; they may be introduced in the 82nd Congress and appear in similar, if not identical, form. It is timely, therefore, to consider the status of certain of the health bills as a guide to the situation that we may expect to see unfold in the newly elected Congress.

COMPULSORY HEALTH INSURANCE

Despite the all-out campaign waged by the AMA and many other powerful organizations, compulsory health insurance will undoubtedly continue to be a storm center. A bill for compulsory health insurance has been introduced, in one form or another, into every Congress since the first Wagner-Murray-Dingle Bill was introduced in 1943. It is not likely that the 82nd Congress will break this chain. Mr. Oscar Ewing has not stepped out of his position as Head of the Federal Security Agency, although the AMA has demanded his resignation in quite unmistakable terms; nor has he abandoned his vigorous support of a system of universal health insurance. In an address on November 19, he said "we must find means to bring the best health services within the financial reach of every man, woman and child; and in my mind, that can best be accomplished through national health insurance as advocated by President Truman." On November 26, in an address before the Harlem Interracial Platform, he ripped into the AMA with the following words: "Are we to haul down our flags and permit the AMA and other reactionary organizations of this country to continue to utilize the present international crisis as a smoke screen for their selfish policy of scarcity in medical personnel?" In this address, he referred to the need for basic health services in local communities; to the "crying need for more hospitals and health centers—particularly in our small towns and rural areas"; to the need for an increase in the supply of doctors, nurses, dentists, and other medical personnel. In reference to the "fundamental question of health insurance" he stated that "a solution to this problem of health and medical care must continue to have an A-1 priority on the nation's order of current business."

The ranks of those members of Congress who have stood for compulsory health insurance and against the AMA have been thinned, but the administration's health program still has many supporters in the 82nd Congress. Conspicuous by their absence will be

Representative Biemiller, who has been an outstanding opponent of the AMA and proponent for government health insurance, and Senator Claude Pepper who was defeated last summer in a Florida primary. It should also be noted that Senator Donnell, the Senate's most persistent foe of compulsory health insurance, was defeated. Senator Murray, whose name has repeatedly appeared in the Murray-Wagner-Dingle Bills, is a likely candidate for Chairmanship of the Labor and Public Welfare Committee to which health legislation is referred in the Senate.

Local Health Units

A bill for local health units has been one of the most noncontroversial bills, and has had favorable, although not final, action in both the 80th and 81st Congress. In the Senate, S. 522 was passed without a dissenting vote in the first session of the 81st Congress. A companion bill, H.R. 5865, was favorably reported by the House Interstate and Foreign Commerce Committee and has been before the Rules Committee since June 1950. A concerted effort is now being made to secure passage of this bill even before the 81st Congress adjourns.

The position of the AMA in regard to the Local Health Units Bill has been somewhat difficult to follow. This legislation has been supported in the House of Delegates by resolutions over the past several years; it has had favorable editorial comment in the *Journal of the American Medical Association;* and local public health service is included in the 12 point program of the AMA. As late as June 20, 1950, the Washington office of the AMA stated in regard to H.R. 5865 "The American Medical Association has approved this bill." In view of its strong power in the past, it is hard to understand the action taken by the House of Delegates in San Francisco in opposing this legislation.

Federal Aid to Medical Education

S. 1453 and H.R. 5940, companion bills, which would provide for federal aid to medical education have been actively considered in both Houses. S. 1453 was passed by the Senate in September 1949. It has received active support from the deans of medical colleges, but at the same time has also been the cause of considerable controversy aroused by the AMA. In December 1949, the Council on Medical Education and Hospitals and the Board of Trustees issued a joint statement on these bills. The matter is set forth in the report of the Council as follows: "This statement listed several criticisms of the bills and concluded that the bills were not satisfactory since they were potentially dangerous to the continued academic freedom of the medical schools. Subsequently, the Council collaborated with the Committee on Legislation in preparing a statement which was issued on January 15, 1950 and which set forth specific recommendations for changes in the proposed legislation that would safeguard academic freedom and make the bills acceptable in the opinion of the Committee on Legislation and the Council.

"The proposals for federal aid to medical education put forth up to the time this report was written have been presented as solutions for a peacetime problem. Discussion and criticism of these proposals has been based on an appraisal of their need and suitability for this purpose. The Council suggests that if facts are accumulated which demonstrate that some form of federal aid to the medical schools is important to the national effort in the current emergency or its sequelae, the medical profession must be ready to restudy and reevaluate this entire problem."*

* J.A.M.A. 144:663 (Oct. 21) 1950.

A new factor has been introduced into the question of federal support of medical and dental schools. As reported by Gerald Gross in the November 27, 1950 *Washington Report on Medical Sciences,* the American Legion has just launched a survey to ascertain "facts and figures on veterans hospitals, need for additional hospital beds, medical manpower shortage, and medical teaching institutions throughout the country . . . as promptly as possible." This particular study therefore concerns itself not only with medical and hospital care, but also with professional manpower. With the full weight of the powerful American Legion behind it, this action may have considerable bearing on Congress's decision on federal aid to medical education.

School Health Services

The companion bills S. 1411 and H.R. 3942 provided for federal grants to aid the states in developing health services for children of elementary and secondary school age. This bill passed the Senate without a dissenting vote and in the House was reported favorably by the Health Sub-Committee of the House Interstate Commerce Committee but the full Committee took no action on the bill. The bill calls not only for periodic medical and dental examinations for all children, but also for treatment of the defects revealed by these examinations. It would be left up to the individual states to determine whether or not this treatment might be given irrespective of the economic status of the parents. This treatment clause permitting curative service to be given without a means test has been the cause of opposition on the part of the medical profession. Nevertheless, this bill which has received considerable Congressional attention in recent years, will undoubtedly appear again with the active support of the American Parents' Committee.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

IRON THERAPY IN HYPOCHROMIC ANEMIA

By EDWIN B. McLEAN, M.D.
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IRON deficiency anemias constitute a large portion of anemias encountered in pediatric practice. Though improvements in diagnostic evalution and in therapy have been made in recent years, the knowledge of the factors involved in the metabolism of iron, such as its absorption, transport, incorporation into hemoglobin and excretion, is far from complete. The availability of radioactive iron in recent years has made possible the development of tracer technics.[1] Studies employing such technics have already provided new information and give promise of adding materially to a clearer understanding of the factors which hinder or assist in iron utilization in health and disease. It is the purpose of this paper to indicate the problems related to iron metabolism in the pediatric age range with the intent that they may provide background for a better understanding of the principles involved in therapy.

Of particular interest to the pediatrician is the store of iron in the infant at the time of birth. Iron is transported across the placenta from the maternal serum iron[2] largely during the last trimester of pregnancy,[2, 3] with the fetus actively storing iron right up until the time of birth. Normally the fetus receives from 300 to 500 mg. of iron from the mother during fetal life.[4,5]

However, when the mother has an iron deficiency anemia during the latter part of pregnancy and thus presents a lowered serum iron concentration to the placenta, the fetus does not obtain its full quota of this metal. Being thus deprived of adequate stores of iron, the newborn infant, although he may have an adequate hemoglobin concentration at birth, faces the ensuing months of rapid growth with the necessity to provide iron for additional hemoglobin formation largely from dietary sources. Since the infant's diet is often limited to milk during these early months and since milk, especially cow's milk, is low in iron content, this source of iron also is inadequate. Under these circumstances an iron deficiency results.[6] This occurs either during the first year, sometime after the fourth month of life, or during the second year.

The obvious conclusion to be drawn from a review of this sequence of events is that prevention of fetal iron deficiency is of prime importance. Thus a careful surveillance of the iron stores of every pregnant woman is necessary. Considering the demands of the fetus and the tendency to hypochlorhydria in pregnancy[7,8] with the resultant poor release of iron from ingested food, it is probably wise to advise a relatively high dietary intake of iron for the mother during gestation. A diet containing iron 16 to 20 mg./day is probably adequate. This can usually be assured when the diet includes one or two

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eggs and one serving of meat per day.[5] If, however, the pregnant woman starts pregnancy with an iron deficiency or develops an iron deficiency during pregnancy, the correction of this state cannot be accomplished solely by improvement in her diet. Here the use of therapeutic iron for the mother, preferably in the ferrous state[9–12] 0.3 g. (5 grains) of ferrous sulfate three times daily, is indicated. Even in the absence of demonstrable deficiency in the mother, if there is a history of multiple pregnancies, menorrhagia or iron deficiency anemia in her last offspring, the use of therapeutic iron during the pregnancy is to be advised. If the iron deficiency is discovered very late in pregnancy, the amount of iron needed to overcome the maternal deficiency and the resultant fetal deficiency can scarcely be provided by iron administered only by the oral route. Under these circumstances saccharated iron oxide can be administered intravenously over a relatively short period of time to replenish the maternal stores.[13] The maternal serum iron level,

TABLE 1

IRON VALUES
COMMERCIAL INFANT FOODS

0–1 mg./100 gm.	1–3 mg./100 gm.	Over 3 mg./100 gm.
Applesauce	Peaches	Prunes (5–9 mg.)
Pears and pineapple	Carrots	Liver (5 mg.)
Pears	Green beans	
Beets	Mixed vegetables	
Squash	Peas	
Custard pudding	Spinach	
	Sweet potatoes	
	Beef	
	Veal	

thus rapidly elevated, would seem to offer a better opportunity for transfer of the needed iron to the fetus. One hundred milligrams of elemental iron can be supplied intravenously to the mother daily until a large portion of the calculated maternal iron deficit is administered. A satisfactory guide for dosage is the administration of 100 mg. for every 4% of hemoglobin deficiency (using 15 gm. Hb./100 cc. = 100%). The remaining iron deficiency can be corrected by oral therapy.

Regardless of the nutritional state of the mother, there is another prophylactic procedure which should be carried out in order to assure the infant his rightful supply of iron. This procedure consists of allowing the umbilical cord to cease pulsating prior to its severance following delivery. This measure will increase the infant's blood supply by about 100 cc. and will thereby add about 45 mg. of iron[14] to the body store. The importance of this procedure can be appreciated when it is realized that this amount of iron is about twice the amount which the average infant retains from his diet during the entire first six months of life.[15]

During the first two months of life, the infant normally exists in a state of negative iron balance.[15] Whether this is due to the inability of the infant to absorb iron at this age or to an insufficient supply of the metal in the diet has not yet been determined. Subsequently, however, food iron begins to contribute to the available iron stores. Although this supply is not great, it is usually sufficient to avert a deficiency state. An infant, if adequately provided with iron during its intrauterine life, will probably not develop any

serious anemia even if kept on a milk diet unsupplemented by additional iron during the entire first year of life.[15] Nevertheless, under these circumstances the hemoglobin concentration at about the third month, the age when the hemoglobin level is apt to be at its lowest, does not provide a reassuring surplus with which to take care of any added load of infection or other emergency which may arise. For this reason it is desirable that the infant's diet contains iron in addition to the limited amount available in milk.[16] Many of the supplementary infant foods contain iron, and the addition of these to the diet at about the third month is desirable. A list of several of the canned strained foods arranged according to their iron content is shown in table 1. However, if the child is a twin or is born of a mother who has had an untreated anemia or who has had a history of

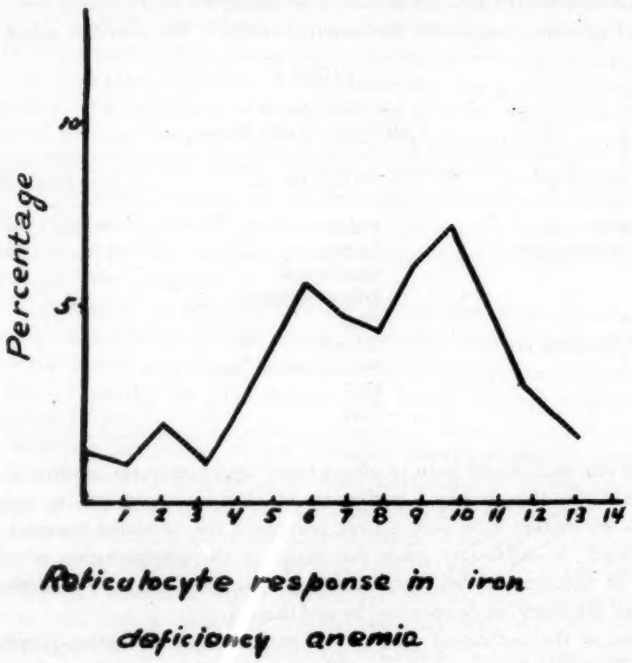

CHART 1.

frequent pregnancies or menorrhagia, or even if the previous child developed an iron deficiency anemia during the first year of life, it is then unsafe to rely upon dietary iron to prevent the anemia.[17] In such instances it is desirable to begin prophylactic iron as soon as the infant can tolerate it. This is generally at about the time orange juice can be begun (3 to 4 weeks of age) and this juice constitutes an ideal vehicle for the iron.[18] The prophylactic dose does not have to be large, 0.15 gm. once daily in the form of an elixir or syrup being satisfactory. If tolerated well, the metal is usually continued through the sixth month of life. At this time therapy can be stopped unless low hemoglobin values necessitate its continuation.

When such prophylactic procedures have not been employed and iron deficiency anemia develops, or when such an anemia develops in spite of them, iron in therapeutic

doses is, of course, indicated. In this case it is necessary to use relatively large doses of the metal, 0.3-0.6 gm. of ferrous sulfate usually being adequate. This salt is best given in liquid form as a syrup or elixir on an empty stomach. It can be given alone, with plain water or with fruit juices. There is no evidence to justify the addition of adjuvant substances to the iron in iron deficiency anemia. While there may be instances where copper is needed, they are rare, and probably a sufficient quantity is present as a contaminant in the usual forms of iron to care for any such deficiency.

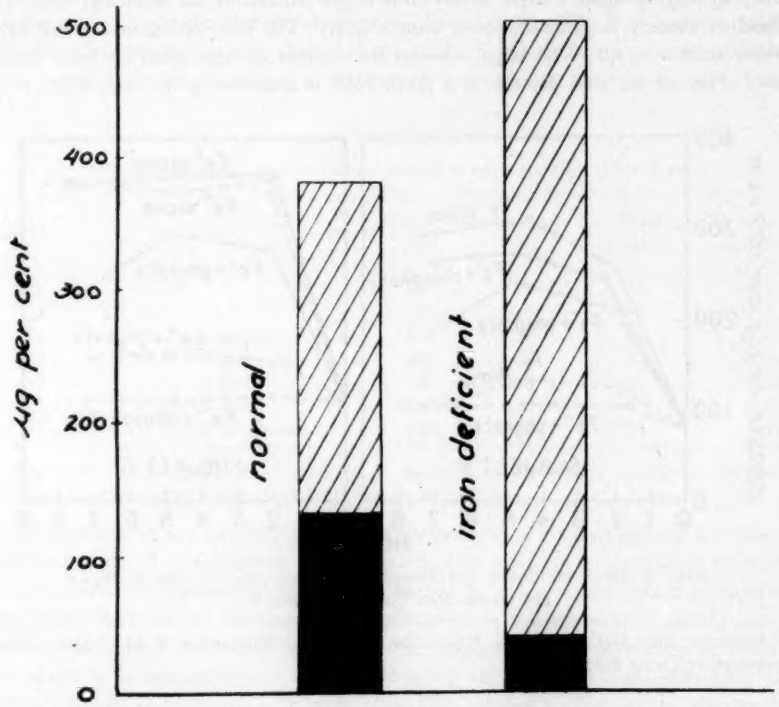

CHART 2. Serum Iron and Iron Binding Protein in Levels in Blood of Normal and Iron Deficient Children.

Height of bar represents total iron binding capacity. Solid portion represents actual serum iron levels.

If the diagnosis has been accurate and a true iron deficiency anemia is present, there will result a reticulocytosis comparable to, although not as great as, that following liver therapy in a patient who has a macrocytic or pernicious anemia (chart 1). If the reticulocyte percentage is plotted daily, a rather smooth curve will result, beginning about 3 to 5 days after the onset of therapy and reaching a maximum in 5 to 6 days. Not infrequently the top of this curve will have a saddle shape. Proof of a satisfactory reticulocyte response depends upon a progressive rise and fall of the curve and is not established by a single elevated reticulocyte percentage a few days after therapy is begun. The reticulocyte determination can be obtained every two days although daily observations are more satisfactory. The confirmation of the diagnosis and the demonstration of the efficacy of

the therapy justify the effort involved in carrying out this procedure. In the child with iron deficiency anemia there is a decrease in the iron concentration of the serum. This is so in spite of the fact that there is an actual increase in the capacity of the blood protein to bind the iron. These changes are illustrated in chart 2. Successful iron therapy corrects these deviations, the serum iron is elevated to its normal level and the capacity of the iron binding protein is appropriately reduced.

It might be well to comment at this point on the possibility of correcting iron deficiency by relying upon a high dietary iron intake instead of on medicinal iron. This method of therapy is generally quite unsatisfactory. The iron deficit in a frank hypochromic anemia is apt to be large, whereas the amount of iron taken up from food is limited. Not all the iron present in a given food is available to the body and of that

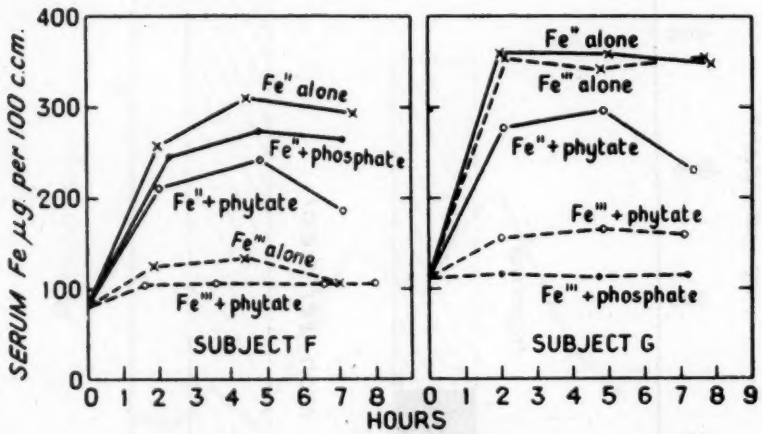

CHART 3. Effect of Phytate and Phosphate on Absorption of Iron as Shown by Serum Iron Tolerance Curves.*

* Abstracted from McCance, R. A., Edgecombe, C. N., and Widdowson, E. M., Phytic acid and iron absorption, Lancet **2**:126, 1943.

available only a part is absorbed.[1,19] In practice it has usually been found necessary to use additional therapeutic iron for satisfactory results.

Not a small part of the limitation in iron absorption from the intestine results from the presence of other food substances in the stomach and duodenum along with the iron. Such substances can inhibit iron absorption to a significant degree. It is known, for example, that phytates, as found in brown bread or oatmeal, will decrease iron absorption.[10,20] This effect was shown by McCance, Edgecombe and Widdowson in 1943,[10] using the iron tolerance curve as an index of absorption. In these experiments the ingestion of a test dose of iron accompanied the phytate containing meal. The height of the serum iron curve was interpreted as a measure of the degree of absorption of the iron. In chart 3 the iron curve following the phytate meal is seen to be lower than the control curve. The effect of phosphates was studied by the same technic. A similar decrease in the iron curve followed the ingestion of a high phosphate meal.

The validity of this use of the serum iron curve for testing the degree of absorption

of iron has been questioned by some. However, Sharpe and his coworkers in 1948[20] re-examined the problem using radioactive iron and confirmed the fact that phytates interfere with iron absorption. These workers also demonstrated that milk interferes with the absorption of iron (table 2). This latter effect may be due to the phosphates contained in the milk. Presumably the mechanism involved in this interference with iron absorption is the formation of insoluble iron phytates or phosphates which remove the iron from a state of availability.

Not too much is known about such interrelations between various food substances and their effect upon the absorption of essential food factors. The findings reported here were made on normal subjects. Whether the blocking effect of phytates and phosphates is an important factor controlling absorption in iron deficient subjects is not yet known.

TABLE 2*

PERCENTAGE OF RADIOACTIVE IRON ABSORBED FROM EXPERIMENTAL MEALS

Meal No.	Food	Wt. of Meal (in mm.) Wet	Dry	Total Subjects	Fe Absorbed per cent
V	Water	200	0	10	26.9
II	Milk	200	26	10	17.4
IV	Milk and oatmeal	373	52	10	9.81
VII	Milk and oatmeal	485	69	10	8.84
VI	Complete meal	766	136	10	5.76
I	Complete meal	744	119	10	4.43
III	Milk and Na phytate	200	26	10	1.74

* Abstracted from Sharpe, L. M., Peacock, W. C., Cooke, R. and Harris, R. S., Effect of phytate and other food factors on iron absorption, J. Nutrition, to be published.

Work underway in our laboratory using radioactive iron is directed towards a more complete evaluation of this problem. One practical conclusion can be arrived at from these considerations: all therapeutic iron should ideally be given to the infant or child at a time when there are no additional food substances in the stomach. It should not, for example, be mixed with milk because of the tendency to the formation of insoluble phosphate. It is not, however, always convenient to administer iron salts to a child without giving them along with some palatable substance. Fortunately, the work of Groen[21] has demonstrated that organic acids, particularly if they are also reducing agents, will maintain the acidity of the duodenal contents at a point which is favorable for iron absorption. For these reasons the common practice of using orange juice as a diluent for the administration of iron seems to be a logical one and, though this procedure has not been tested with radioactive iron technic for exact confirmation, its wide clinical use speaks in favor of it.

The anemia of prematurity presents a somewhat difficult problem. At the onset this anemia is not one of iron deficiency; however, it may later lead to iron deficiency because during the period of the natural recovery from this anemia the rate of and degree of increase in red cell mass is so great that the iron stores of the infant may be insufficient to supply the necessary hemoglobin. In view of these considerations, iron therapy during this recovery phase would seem to be indicated. Unfortunately, information regarding the ability of the premature infant to absorb such therapeutic iron at least in the first few

months of life is inadequate. There can be no harm, nevertheless, in adding such iron when the diet is established sufficiently well to enable the infant to tolerate it. Its administration with orange juice is satisfactory. A dose of 0.15 gm. of the ferrous sulfate daily is ample. In the Pediatric Department at Temple University Hospital, it is the custom to give the premature infant a transfusion if the hemoglobin drops below 8 gm./100 cc. or the erythrocyte count below RBC 3.0 million/cmm.

In children iron deficiency not infrequently occurs in association with the anemia of infection. Probably the deficiency in this case is largely accounted for by: (1) inadequate intake due to poor appetite and (2) failure of the stomach to hydrolyze the food adequately for the proper release of absorbable iron. This latter may be related to the temporary hypochlorhydria which often accompanies infection.[22] The administration of therapeutic quantities of iron, in these instances, usually fails to overcome the anemia. Even that element of the anemia due to iron deficiency may not be corrected. This apparently is due not to failure of absorption of iron[19] but to a failure of the erythropoietic tissue to incorporate the iron into hemoglobin.[23]

When severe enough to demand therapy, the anemia of infection whether or not complicated by iron deficiency is best treated by transfusions. The donor red cells so administered not only increase the oxygen transport facilities but, when their life span is completed, provide additional iron to the child. Each 100 cc. given in this manner supplies about 45 mg. of elemental iron. During convalescence from infection when anemia has been conspicuous, iron orally administered may be indicated to correct any residual hypochromic anemia.

Most iron deficiency anemias of infancy are due to the causes which have just been discussed. Occasionally, of course, chronic blood loss is responsible. This cause is much less frequent, however, than in the adult. The primary treatment in such instances is that of the lesion responsible for the loss, e.g., bleeding from the skin in a chronic eczema or an intestinal polyp. Furthermore, the character of the lesion or its surgical treatment frequently necessitate transfusions which take care of the immediate need for hemoglobin. Nevertheless, the use of ferrous sulfate in therapeutic doses of 0.3 to 1.0 gm. daily depending upon the weight of the child usually is desirable during convalescence in order to replenish depleted iron stores.

Occasionally chronic gastrointestinal disease interferes with proper iron absorption. Diseases such as celiac disease, congenital malformation and postoperative shunts of the gastrointestinal tract are in this class. Here the oral use of therapeutic doses of iron, although usually satisfactory, may result in further gastrointestinal symptoms. Transfusions are therefore often necessary. Transfusions, however, because of the occurrence of annoying reactions and the possibility of developing undesirable sensitization when often repeated, may present a problem. In such instances the use of intravenous saccharated iron oxide to supply the iron deficit may be advisable. The total dosage to be administered depends upon the calculation of the iron deficit of the child. This calculation is based upon the drop in hemoglobin concentration. The total number of milligrams of elemental iron needed to correct the deficiency is determined from the following formula:

Deficiency of iron in mg. = BW (16-1.3 Hgb.)
Where BW = the body weight in pounds, and,
Hgb. = the hemoglobin in gm./100 cc.

The preparations of saccharated iron oxide available at present contain iron 100 mg./5 cc. ampul. The parenteral administration of iron should, of course, be limited in amount to approximate the iron deficit. There is no advantage in the administration of larger quantities and there is possible some danger in so doing.

Summary

From the foregoing, it is evident that the first approach to the problem of iron deficiency anemia in infancy is one of prevention. It is essential to obtain the cooperation of the obstetrician in preventing iron deficiency during pregnancy and in allowing the newborn infant to receive as much of the placental blood as possible. When a deficiency is known to have been present in the mother during pregnancy, it is advisable to administer adequate doses of iron to the infant during the early months of life. Iron therapy for the infant or child who has already developed iron deficiency should be provided in adequate amounts. Dietary iron alone should not be relied upon to bring about recovery. Iron therapy will not prevent the anemia of prematurity but may be helpful in preventing the deficiency of this metal which can develop during recovery therefrom. Transfusions when indicated in the anemia of infection will supply needed iron to care for any associated iron deficiency. Iron deficiency due to chronic hemorrhage demands therapy directed toward the primary cause. In chronic gastrointestinal disease orally administered iron may not be well tolerated and repeated transfusions may be contraindicated. In these rare instances intravenously administered iron is a valuable therapeutic agent.

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227 Brockius Avenue

SPECIAL ARTICLE

LEGIBLE LANTERN SLIDES

By RICHARD M. HEWITT, M.D.
Rochester, Minn.

PHYSICIANS commonly complain that many of the characters projected from stereopticon slides at medical meetings are too small to be read. One physician had been sufficiently annoyed by illegible projections to suggest that an exhibit be prepared to demonstrate the causes of, and the remedy for, the difficulty. This was done.

The main parts of the exhibit were two frames (Figs. 1 and 2). Figure 1 was intended to demonstrate that, as the number of characters in the copy becomes smaller, each projected character becomes larger and thus more legible.

Figure 2 was planned to help the speaker who might object: "True. But what I have to present takes a lot of characters; what can I do about that?" Herein figure 2 is broken down to the essentials of the four panels of which the frame was composed.

A subsidiary part of the exhibit had to do with what might be dignified as the related forensics. It occupied the two wings of the booth. On one wing appeared the jingle:

He never was heard
And never was seen,
Who turned in the dark
And read from the screen.

On the other wing, the corresponding rhyme read:

His audience yawned,
It squirmed and it sighed;
He constantly put
Too much on a slide.

It may be helpful to add that a detailed table, suitable for publication, may be unsuitable for a slide. Slides are exhibits, and one principle of exhibiting is to eliminate all possible reading matter.

From an exhibit presented at the Annual Meeting of the American Academy of Pediatrics, San Francisco, Nov. 14 to 17, 1949.

From the Section on Publications, Mayo Clinic, and the Museum of Hygiene and Medicine, Mayo Foundation, Rochester, Minn.

(Received for publication Sept. 29, 1950.)

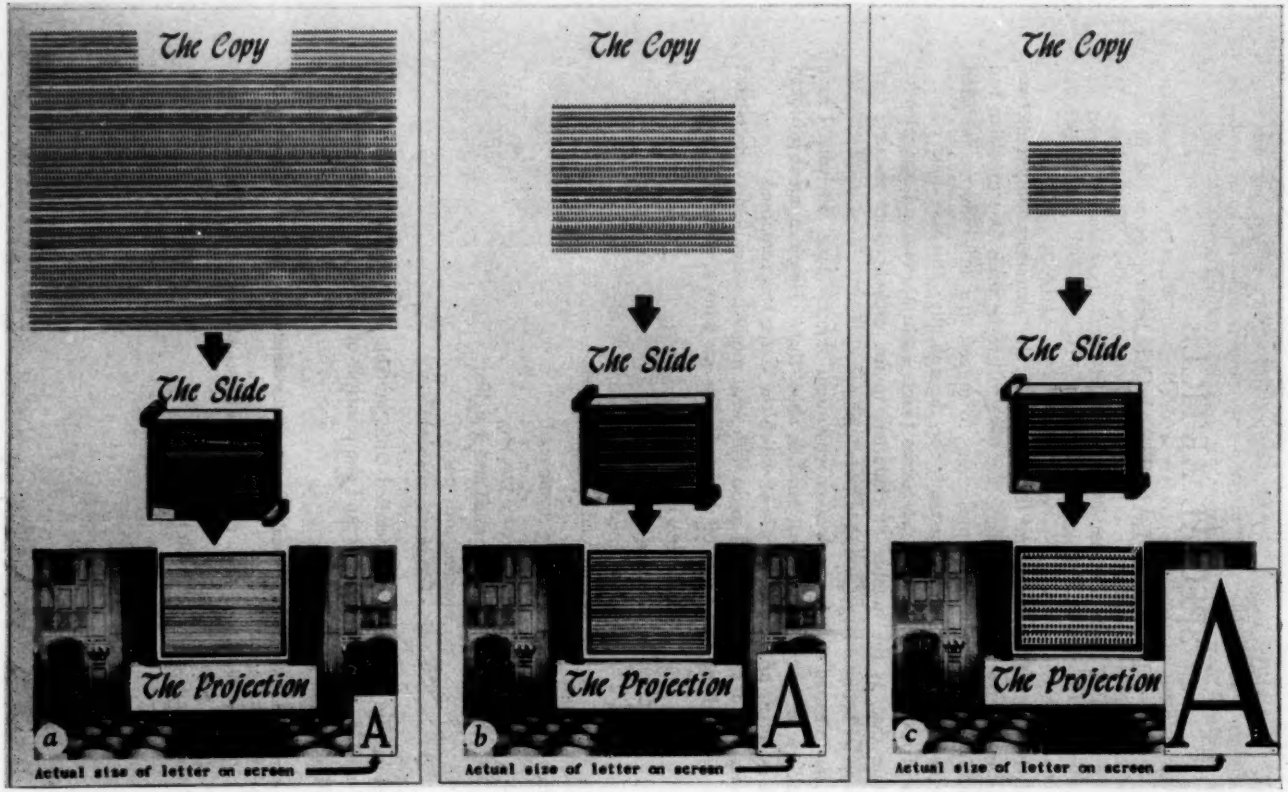

FIG. 1. The fewer the characters in the copy, the larger each character appears on the screen. The foregoing assumes that the dimensions of the copy will be proportional to those of a slide.

a. Under the experimental conditions employed, 48 lines of copy, composed of approximately 4800 characters, when photographically reduced to crowd the material within the inflexible dimensions of a slide, yielded characters only 1¼ inches high on the screen.

b. Twenty-four lines of copy, composed of approximately 1200 characters, yielded characters approximately 2½ inches high on the screen.

c. Twelve lines of copy, composed of approximately 300 characters, needed no photographic reduction in making of the slide, and yielded characters approximately 5 inches high on the screen.

Table 1
Summary of cases in which drug A was given

Diagnosis	Total dose Gm.	Days Organism	A. Effect of drug B. Final result	Toxicity	Accessory therapeutic measures
Perineal cellulitis	49	17 Streptococcus,	A. Questionable		Transfusions
	24.2	9 anaerobic	B. Uncured	None*	Local treatment

Table 1 (continued)

Diagnosis	Total dose Gm.	Days Organism	A. Effect of drug B. Final result	Toxicity	Accessory therapeutic measures
Chronic ulcerative colitis	90	28 Unknown	A. Favorable	Peripheral neuritis	None
			B. Improvement		
Chronic ulcerative colitis	67	15 Unknown	A. Favorable (temporary)	Peripheral neuritis	None
	63	15	B. Uncured		
Chronic ulcerative colitis	36	7 Unknown	A. Favorable	None	None
			B. Improvement		
Chronic ulcerative colitis	42	12 Unknown	A. Favorable	None	None
			B. Improvement		
Pacilluria	10.2	7 Escherichia coli	A. Favorable	None	None
			B. Recovery		
Bacilluria	7	3 Escherichia coli	A. Favorable	None	None
			B. Recovery		
Bacilluria	10.6	4 Proteus	A. Favorable	None	None
			B. Recovery		
Bacilluria	48.2	16 Proteus	A. Favorable	None*	None
			B. Recovery		
Bacilluria; left renal calculus	44	11 Escherichia coli	A. Favorable	None*	None
			B. Recovery		Right middle lobectomy
Bronchiectasis; tuberculosis; pneumonitis	27	9 Staphylococcus aureus; Gram-negative bacillus	A. Favorable		Transfusions
			B. Recovery	None	Frontal sinus drilled later
Gonorrheal urethritis	36.6	7 Neisseria gonorrhoeae	A. Favorable	None*	None
			B. Recovery		
Fever of unknown origin	21	7 Unknown	A. Favorable	None*	Previous sulfanilamide
	72.6	49	B. Temporary improvement		
Fever of unknown origin	49.8	11 Unknown	A. Favorable	None*	None
			B. Temporary improvement		

*denotes previous intolerance to sulfanilamide. (When one dose of the drug was given on the first day this was counted as one day in the table.)

SUMMARY OF TOXIC EFFECTS IN RELATION TO DRUG A: 32 CASES

Cases	Toxic effect
21	None.
7	None with drug A but previous intolerance to sulfanilamide.
4	Toxic manifestations with drug A: a. Mild tinnitus and vertigo. b. Peripheral neuritis. c. Peripheral neuritis. d. Fever, dermatitis and cyanosis.

FIG. 2a

FIG. 2. To reduce the number of characters, details must be deleted. In each of the 4 panels shown (a, b, c and d) the material at the top represents the raw material; that at the bottom represents the copy for a slide that was developed from the raw material.

Detail of figure 2a. The raw material (upper portion) consisted of 2 sheets almost full of tabular data concerning a series of cases. Here, of necessity, the second sheet lies on top of the first and almost obscures it. To reduce the material to a size suitable for a slide, the raw data were studied until the important points became apparent. These were that drug A seldom was toxic and that, when it was toxic, the manifestations were thus and so. Then the material was condensed to give the evidence necessary to support the foregoing points—and nothing else.

characters approximately 5 inches high on the screen.

Data on six cases of Hodgkin's disease of the stomach

Case	Age	Sex	Temperature	Presenting symptoms	Hb	RBC	WBC	Gastric acidity	Glandular involvement and RX	Course
1	44	M	97.6	P.C. distress in mid epigastrium with relief 2 yrs.; constant epigastric pain 2 mo. 20 lb. weight loss	72	3.98	6,600	Achlorhydria	Total gastrectomy; with no glandular involvement detectable at surgery	Died 6 days later. P.O. pneumonia
2	62	M	97	Vomiting 6 mo.; 4 weeks nocturnal epigastric pain; food and soda relief. Mass left upper quadrant. 26 lb. weight loss	70	4.26	10,300	Normal	Partial resection with glandular involvement	Patient living 6 yr. postoperatively
3	47	M	98	Epigastric pain periodic 6 yr. Constant distress in epigastrium 1½ yr. 14 lb. weight loss	77	4.80	6,100	Normal	Partial resection with glandular involvement	Patient living 6 yr. postoperatively
4	48	M		Weight loss 70 lb. in two years. Loss of strength and appetite	81	3.74	14,100	Normal	Partial gastrectomy & x-ray therapy subsequently with glandular involvement	Died 3 mo. postoperatively
5	30	M	98.3	Peptic ulcer story 8 months; migraine headaches 1½ years. No weight loss	96	4.26	6,800	Normal	Simple excision of ulcer. No glandular involvement	Living 6 yr. postoperatively
6	62	M	97	Epigastric pain of 6 weeks duration. No weight loss	80		10,600	Normal	Partial gastrectomy. No glandular involvement	Living one year postoperatively

OUTSTANDING FACTS CONCERNING 6 CASES OF GASTRIC HODGKIN'S DISEASE

Age: Prevailingly fifth and sixth decades.
Sex: Males.
Temperature: Normal.
Symptoms and signs: Epigastric pain after meals relieved by food and soda; loss of weight.
Blood: Mild microcytic anemia.
Gastric acidity: Normal (5 cases); achlorhydria (1 case).
Treatment: Ranged from simple excision to complete gastrectomy.
Involvement of lymph nodes: Present in 50 per cent of cases.
Survival: Average 4 years +.

FIG. 2b

REPORT OF CASE 14

History and physical examination.-- A woman, twenty-one years old and a student at the University of Oklahoma, was examined at the Mayo Clinic in February, 1936. For three or four years she had had headaches involving the occipital and frontal areas which had gradually increased in frequency until they occurred almost every day. The year previous to examination she had tired easily, had dyspnea with exertion, episodes of dizziness, nocturia two to three times and transient pains in the left thorax occurring during rest and exercise. Insomnia had been present for seven months. Three months before examination at the Clinic, examination for fitness for athletics at the University disclosed severe hypertension. The physical examination was essentially negative except for hypertension, slight thickening of the radial arteries, and moderate narrowing and spasm of the retinal arteries.

REPORT OF CASE 14

History and physical examination
Women, 21 yrs. old, student, examined at Mayo Clinic Feb. 1936
For 3 or 4 yrs. before exam.: occipital and frontal aches; increased in frequency to almost every day
For 1 yr. before exam.: fatigue, dyspnea on exertion, dizziness, nocturia, transient pain left thorax during rest or exercise
For 7 mo. before exam.: insomnia 3 mo. before exam.: severe hypertension discovered elsewhere
Exam. at clinic: hypertension, slight thickening radial arteries, moderate narrowing and spasm of retinal arteries

FIG. 2c

VOLUME OF EYEBALL OF NEWBORN INFANT

Bulbar segment (major segment of a sphere):

$V=\frac{1}{3}\pi h^2 (3R - h)$

$V=1.0472 \times (16.7 - 3)^2 \times [3 \times (\frac{16.4}{2}) - (16.7 - 3)] = 2260.3 \text{ mm}^3$

Corneal segment (minor segment of a sphere):

$V=\frac{1}{3}\pi h^2 (3R - h)$

$V=1.0472 \times (3)^2 \times [3 \times (\frac{14}{2}) - 3] = 169.7 \text{ mm}^3$

Calculated, corrected volume of eyeball. Volume of a major segment sphere + volume of a minor segment sphere.

$V=2260.3 + 169.7 = 2430.0 \text{ mm}^3$

Courtesy Hilmer and Scammon

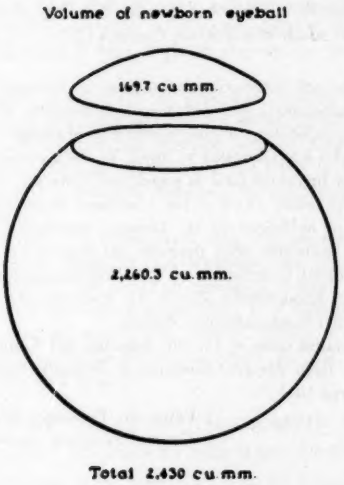

FIG. 2d

Detail of figure 2b. The raw material (upper portion) consisted of a detailed table concerning a series of cases. The principle employed was to run the column heads of the table down the left hand side of the slide and to summarize each column on the same line as the corresponding heading. With the help of condensation, elimination of repetition, and a little change in headings, this was effected. Almost always tabular data on a series of cases are susceptible of this treatment for presentation on a slide. Perhaps the most conspicuous condensation here was effected when 3 columns of numerical data on the blood were replaced by the words "mild microcytic anemia."

Detail of figure 2c. The raw material (upper portion) was a report of a case in running text. The material was classified, condensed from 136 to 81 words, and interlined. The lines furnish goals for the eyes and mind of a reader in the audience.

Detail of figure 2d. The raw material (upper portion) consisted of a mathematical expression difficult for many to understand. It was replaced by a picture.

Section on Publications, Mayo Clinic

NEWS AND ANNOUNCEMENTS

The Boston Floating Hospital, the Pediatric Teaching Unit of the New England Medical Center, announces the appointment of Dr. Orvar Swenson as Surgeon in Chief on October 15, 1950. Dr. Swenson has also been appointed Associate Professor of Surgery in the Tufts College Medical School.

* * *

The Pediatric Cardiology Department of the Children's Division of the Cook County Hospital is now accepting applications for fellowships for immediate appointment. The department offers large material of both congenital and acquired diseases of the heart. Over 500 cases of congenital malformations of the heart have been studied in the past 3 years. There is a complete department of angiocardiography and catheterization. Salary commensurate with experience.

Please write to Dr. Rowine H. Brown, Assistant Medical Superintendent, Children's Division of the Cook County Hospital, 700 South Wood Street, Chicago 12.

* * *

The third pamphlet of the 6th International Congress of Paediatrics, with the missing abstracts of lectures and all the communications and discussions, is finished. This volume will be sent to the different national paediatric associations for distribution free of charge among the conference members with cards series A and C who are requested to apply to their paediatric association in this matter.

All those interested in this literature such as physicians, libraries, clinics, a.s.o., may obtain either the 3 single volumes for Swiss francs 25.— or the 3 volumes bound together for Swiss francs 27.—. The congress transactions will be edited by the General Secretary's office, International Paediatric Association, and sent to the applicants after payment has been received. If more than 10 copies of the whole transactions are ordered, a reduction of 30% will be granted. Orders may be forwarded to the General Secretary's Office, Kinderspital, Zürich 32. Payments should be made to the account of the association with the "Zürcher Kantonalbank," Zürich.

A certain number of the transactions of the 5th International Congress of Paediatrics, New York 1947, may still be obtained from Messrs. Almquist & Wiksell, Editors, Upsala, Sweden, for the reduced price of Swedish crowns 10.—.

PROF. G. FANCONI, M.D.,
General Secretary, International Paediatric Association

BOOK REVIEWS

THE COMMON INFECTIOUS DISEASES, H. Stanley Banks, M.A., M.D., F.R.C.P., D.P.H., Baltimore, Williams & Wilkins Company, 1949, $4.50, 354 pp., with illustrations.

Few faults are likely to be found in this treatise even by the most severe critic. However, in the preface the British author seems to imply that he was the original promotor of certain "new ideas, methods and modifications of established practice." In this connection, he refers to his advocacy of intravenous antitoxin for severe cases of diphtheria, a method which was used routinely by Dupaquier at the Charity Hospital in New Orleans as early as 1915 and strongly recommended by Mixsell of New York a few years later. And "the short isolation period in scarlet fever" was resorted to by Milne of Britain more than 40 years ago and put into effect by Gordon while at Herman Kiefer Hospital in Detroit about 1930. Also, in this country, Hoyne has consistently opposed intrathecal therapy for meningitis for at least 15 years and advised lumbar puncture only for diagnostic purposes.

There are 17 chapters which embrace all the principal common contagious diseases. A brief chapter relating to Acute Diarrhea in Infants and one concerning Infective Gastro-Enteritis of Infants are also important. Diphtheria receives special attention with an Appendix: Electrocardiography in Diphtheria by L. J. M. Laurent. Although diphtheria is discussed in an unusually able manner the subject of intubation is dismissed in 3 sentences. However, the chapters on Diphtheria and Whooping Cough are particularly outstanding.

At the close of each chapter there is a bibliography and cross references are numerous throughout. There are many illustrations, some depicting skin eruptions, and other photographs of roentgenograms disclosing areas of collapse of the lungs in whooping cough.

The book is well written and thoroughly up to date. It is readily apparent that the author is fully conversant with the practical as well as the scientific aspects of the acute infectious diseases. A general index provides easy accessibility for special topics and the volume is of convenient size. The book should be exceptionally well received.

BIBLIOGRAPHY ON THE PSYCHOLOGY OF THE HANDICAPPED, National Society for Crippled Children and Adults, Inc., 11 South La Salle Street, Chicago.

A selection of titles in the library of the National Society for Crippled Children and Adults, this bibliography on psychology of the handicapped had been compiled for students and all professional workers seeking information on the subject. Copies may be obtained without cost by writing to the National Society.

TOS FERINA (Whooping Cough), Jerónimo Pou Díaz, M.D., Zaragoza, Spain, 1949, 320 pesetas ($8.00), 294 pp.

This volume is a review of pertussis—its history, etiology, bacteriology, epidemiology, immunity, pathology, diagnostic problems and tests, clinical studies and treatment, based on an extensive review of the literature (706 references) and the clinical experience of the author.

EDITORIAL

THE Editorial Board of PEDIATRICS announces two changes of personnel with the New Year of 1951. These changes have been approved by the Executive Board of the Academy at its meeting at Chicago, October 16-19, 1950. Dr. Grover F. Powers, New Haven, and Dr. Irvine McQuarrie, Minneapolis, have been retired from the Board and Dr. Milton J. E. Senn, New Haven, and Dr. Mitchell I. Rubin, Buffalo, have been appointed to the Board effective January 1, 1951.

Dr. Powers and Dr. McQuarrie have been on the Editorial Board since the creation of the Board for PEDIATRICS and both served on the Board of the *Journal of Pediatrics* almost from the beginning of that publication. They have both been of invaluable assistance in guiding the early career of PEDIATRICS. Dr. McQuarrie, through his intimate knowledge of publication procedures, contributed a great deal of his time and ability toward getting PEDIATRICS "started." His services will be missed and his wise advice on many subsequent points is appreciated. On behalf of the Academy and the Editorial Board this acknowledgement is made to Dr. Powers and Dr. McQuarrie. Readers of PEDIATRICS may not have recognized the influence of these two editors where it has been merged and hidden in the total character of the publication, but the Editorial Board has been constantly conscious of this influence. It will be enduring in the future.

Dr. Senn has been of great assistance already in editorial procedures so that his appearance on the Board is more formal and public than actual. His position in pediatrics as a teacher and investigator is well known. He has guided the Academy many times in the field of child guidance, mental health and psychiatry, and is now Chairman of the Academy's Section on Mental Growth and Development. He has also served incognito in the editorial work of PEDIATRICS. It is certain that his position on the Board will be appreciated and approved by everyone. He will continue to deal with his special field of interest.

Dr. Rubin, too, has served incognito on editorial procedures in the field of his special interest but Dr. Rubin's interests are very broad. He should bring to the Board a viewpoint that will be valuable in those fields. His training as a practitioner of pediatrics, as a teacher and investigator should fit him for broad use of these skills in editorial work.

Both Dr. Senn and Dr. Rubin should round out even more the composition of the Editorial Board to embrace all the interests of pediatrics. The Editorial Board welcomes these new members and is proud to announce their appointment.